HALOACETAMIDE AND AZIDE SUBSTITUTED COMPOUNDS AND METHODS OF USE THEREOF

CROSS REFERENCE TO RELATED APPLICATIONS

[0001] This Application claims priority of US Serial No. 10/084,678, filed February 28, 2002, which is hereby incorporated by reference.

GOVERNMENT INTEREST STATEMENT

[0002] This invention was made in whole or in part with government support under grant number R29 CA068096 awarded by the National Cancer Institute, National Institute of Health, and under grant number R15 HD35329, awarded by the National Institute of Child Health and Human Development, National Institute of Health. The government may have certain rights in the invention.

FIELD OF INVENTION

[0003] The present invention relates to androgen receptor targeting agents (ARTA), which contain a haloacetamide or azide moiety and are alkylating agents. These agents are useful for a) male contraception; b) treatment of a variety of hormone-related conditions, for example conditions associated with Androgen Decline in Aging Male (ADAM); c) treatment of conditions associated with Androgen Decline in Female (ADIF); d) treatment and/or prevention of acute and/or chronic muscular wasting conditions; e) preventing and/or treating dry eye conditions; f) oral androgen replacement therapy; g) decreasing the incidence of, halting or causing a regression of prostate cancer; and/or h) inducing apoptosis in a cancer cell.

BACKGROUND OF THE INVENTION

[0004] The androgen receptor ("AR") is a ligand-activated transcriptional regulatory protein that mediates induction of male sexual development and function through its activity with endogenous androgens. Androgens are generally known as the male sex hormones. The androgenic hormones are steroids which are produced in the body by the testes and the cortex of the adrenal gland or can be synthesized in the laboratory. Androgenic steroids play an important role in many physiologic processes, including the development and maintenance of male sexual characteristics such as muscle and bone

mass, prostate growth, spermatogenesis, and the male hair pattern (Matsumoto, Endocrinol. Met. Clin. N. Am. 23:857-75 (1994)). The endogenous steroidal androgens include testosterone and dihydrotestosterone ("DHT"). Testosterone is the principal steroid secreted by the testes and is the primary circulating androgen found in the plasma of males. Testosterone is converted to DHT by the enzyme 5 alpha-reductase in many peripheral tissues. DHT is thus thought to serve as the intracellular mediator for most androgen actions (Zhou, et al., Molec. Endocrinol. 9:208-18 (1995)). Other steroidal androgens include esters of testosterone, such as the cypionate, propionate, phenylpropionate, cyclopentylpropionate, isocarporate, enanthate, and decanoate esters, and other synthetic androgens such as 7-Methyl-Nortestosterone ("MENT') and its acetate ester (Sundaram et al., "7 Alpha-Methyl-Nortestosterone(MENT): The Optimal Androgen For Male Contraception," Ann. Med., 25:199-205 (1993) ("Sundaram")). Because the AR is involved in male sexual development and function, the AR is a likely target for effecting male contraception or other forms of hormone replacement therapy.

[0005] Worldwide population growth and social awareness of family planning have stimulated a great deal of research in contraception. Contraception is a difficult subject under any circumstance. It is fraught with cultural and social stigma, religious implications, and, most certainly, significant health concerns. This situation is only exacerbated when the subject focuses on male contraception. Despite the availability of suitable contraceptive devices, historically, society has looked to women to be responsible for contraceptive decisions and their consequences. Although concern over sexually transmitted diseases has made men more aware of the need to develop safe and responsible sexual habits, women still often bear the brunt of contraceptive choice. Women have a number of choices, from temporary mechanical devices such as sponges and diaphragms to temporary chemical devices such as spermicides. Women also have at their disposal more permanent options, such as physical devices including IUDs and cervical caps as well as more permanent chemical treatments such as birth control pills and subcutaneous implants. However, to date, the only options available for men include the use of condoms and vasectomy. Condom use, however is not favored by many men because of the reduced sexual sensitivity, the interruption in sexual spontaneity, and the significant possibility of pregnancy caused by breakage or misuse. Vasectomies are also

not favored. If more convenient methods of birth control were available to men, particularly long-term methods which require no preparative activity immediately prior to a sexual act, such methods could significantly increase the likelihood that men would take more responsibility for contraception.

[0006] Administration of the male sex steroids (e.g., testosterone and its derivatives) has shown particular promise in this regard due to the combined gonadotropin-suppressing and androgen-substituting properties of these compounds (Steinberger et al., "Effect of Chronic Administration of Testosterone Enanthate on Sperm Production and Plasma Testosterone, Follicle Stimulating Hormone, and Luteinizing Hormone Levels: A Preliminary Evaluation of a Possible Male Contraceptive, Fertility and Sterility 28:1320-28 (1977)). Chronic administration of high doses of testosterone completely abolishes sperm production (azoospermia) or reduces it to a very low level (oligospermia). The degree of spermatogenic suppression necessary to produce infertility is not precisely known. However, a recent report by the World Health Organization showed that weekly intramuscular injections of testosterone enanthate result in azoospermia or severe oligospermia (i.e., less than 3 million sperm per ml) and infertility in 98% of men receiving therapy (World Health Organization Task Force on Methods And Regulation of Male Fertility, "Contraceptive Efficacy of Testosterone-Induced Azoospermia and Oligospermia in Normal Men," Fertility and Sterility 65:821-29 (1996)).

[0007] A variety of testosterone esters have been developed which are more slowly absorbed after intramuscular injection and thus result in greater androgenic effect. Testosterone enanthate is the most widely used of these esters. While testosterone enanthate has been valuable in terms of establishing the feasibility of hormonal agents for male contraception, it has several drawbacks, including the need for weekly injections and the presence of supraphysiologic peak levels of testosterone immediately following intramuscular injection (Wu, "Effects of Testosterone Enanthate in Normal Men: Experience From a Multicenter Contraceptive Efficacy Study," Fertility and Sterility 65:626-36 (1996)).

[0008] Steroidal ligands which bind the AR and act as androgens (e.g. testosterone enanthate) or as antiandrogens (e.g. cyproterone acetate) have been known for many years and are used clinically (Wu 1988). Although nonsteroidal antiandrogens are in clinical use for hormone-dependent prostate cancer, nonsteroidal androgens have not been reported. For this reason, research on male contraceptives has focused solely on steroidal compounds.

[0009] Prostate cancer is one of the most frequently occurring cancers among men in the United States, with hundreds of thousands of new cases diagnosed each year. Unfortunately, over sixty percent of newly diagnosed cases of prostate cancer are found to be pathologically advanced, with no cure and a dismal prognosis. One approach to this problem is to find prostate cancer earlier through screening programs and thereby reduce the number of advanced prostate cancer patients. Another strategy, however, is to develop drugs to prevent prostate cancer. One third of all men over 50 years of age have a latent form of prostate cancer that may be activated into the life-threatening clinical prostate cancer form. The frequency of latent prostatic tumors has been shown to increase substantially with each decade of life from the 50s (5.3-14%) to the 90s (40-80%). The number of people with latent prostate cancer is the same across all cultures, ethnic groups, and races, yet the frequency of clinically aggressive cancer is markedly different. This suggests that environmental factors may play a role in activating latent prostate cancer. Thus, the development of treatment and preventative strategies against prostate cancer may have the greatest overall impact both medically and economically against prostate cancer.

[00010] Osteoporosis is a systemic skeletal disease, characterized by low bone mass and deterioration of bone tissue, with a consequent increase in bone fragility and susceptibility to fracture. In the U.S., the condition affects more than 25 million people and causes more than 1.3 million fractures each year, including 500,000 spine, 250,000 hip and 240,000 wrist fractures annually. Hip fractures are the most serious consequence of osteoporosis, with 5-20% of patients dying within one year, and over 50% of survivors being incapacitated. The elderly are at greatest risk of osteoporosis, and the problem is therefore predicted to increase significantly with the aging of the population.

Worldwide fracture incidence is forecasted to increase three-fold over the next 60 years, and one study estimated that there will be 4.5 million hip fractures worldwide in 2050.

[00011] Women are at greater risk of osteoporosis than men. Women experience a sharp acceleration of bone loss during the five years following menopause. Other factors that increase the risk include smoking, alcohol abuse, a sedentary lifestyle and low calcium intake. However, osteoporosis also occurs frequently in males. It is well established that the bone mineral density of males decrease with age. Decreased amounts of bone mineral content and density correlates with decreased bone strength, and predisposes to fracture. The molecular mechanisms underlying the pleiotropic effects of sex-hormones in non-reproductive tissues are only beginning to be understood, but it is clear that physiologic concentrations of androgens and estrogens play an important role in maintaining bone homeostasis throughout the life-cycle. Consequently, when androgen or estrogen deprivation occurs there is a resultant increase in the rate of bone remodeling that tilts the balance of resorption and formation to the favor of resorption that contributes to the overall loss of bone mass. In males, the natural decline in sex-hormones at maturity (direct decline in androgens as well as lower levels of estrogens derived from peripheral aromatization of androgens) is associated with the frailty of bones. This effect is also observed in males who have been castrated.

[00012] Androgen decline in the aging male (ADAM) refers to a progressive decrease in androgen production, common in males after middle age. The syndrome is characterized by alterations in the physical and intellectual domains that correlate with and can be corrected by manipulation of the androgen milieu. ADAM is characterized biochemically by a decrease not only in serum androgen, but also in other hormones, such as growth hormone, melatonin and dehydroepiandrosterone. Clinical manifestations include fatigue, depression, decreased libido, sexual dysfunction, erectile dysfunction, hypogonadism, osteoporosis, hair loss, obesity, sarcopenia, osteopenia, benign prostate hyperplasia, anemia, alterations in mood and cognition and prostate cancer.

[00013] Androgen Deficiency in Female (ADIF) refers to a variety of hormone-related conditions including, common in females after middle agest. The syndrome is

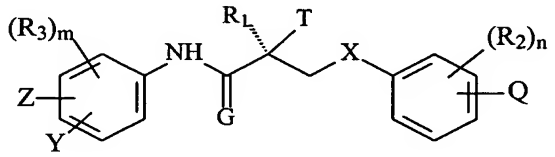
characterized by sexual dysfunction, decreased sexual libido, hypogonadism, sarcopenia, osteopenia, osteoporosis, alterations in cognition and mood, anemia, depression, anemia, hair loss, obesity, endometriosis, breast cancer, uterine cancer and ovarian cancer.

[00014] Muscle wasting refers to the progressive loss of muscle mass and/or to the progressive weakening and degeneration of muscles, including the skeletal or voluntary muscles, which control movement, cardiac muscles, which control the heart (cardiomyopathics), and smooth muscles. Chronic muscle wasting is a chronic condition (i.e. persisting over a long period of time) characterized by progressive loss of muscle mass, weakening and degeneration of muscle. The loss of muscle mass that occurs during muscle wasting can be characterized by a muscle protein breakdown or degradation. Protein degradation occurs because of an unusually high rate of protein degradation, an unusually low rate of protein synthesis, or a combination of both. Protein degradation, whether caused by a high degree of protein degradation or a low degree of protein synthesis, leads to a decrease in muscle mass and to muscle wasting. Muscle wasting is associated with chronic, neurological, genetic or infectious pathologies, diseases, illnesses or conditions. These include Muscular Dystrophies such as Duchenne Muscular Dystrophy and Myotonic Dystrophy; Muscle Atrophies such as Post-Polio Muscle Atrophy (PPMA); Cachexias such as Cardiac Cachexia, AIDS Cachexia and Cancer Cachexia, malnutrition, Leprosy, Diabetes, Renal Disease, Chronic Obstructive Pulmonary Disease (COPD), Cancer, end stage Renal failure, Emphysema, Osteomalacia, HIV Infection, AIDS, and Cardiomyopathy, In addition, other circumstances and conditions are linked to and can cause muscle wasting. These include chronic lower back pain, advanced age, central nervous system (CNS) injury, peripheral nerve injury, spinal cord injury, chemical injury, central nervous system (CNS) damage, peripheral nerve damage, spinal cord damage, chemical damage, burns, disuse deconditioning that occurs when a limb is immobilized, long term hospitalization due to illness or injury, and alcoholism. Muscle wasting, if left unabated, can have dire health consequences. For example, the changes that occur during muscle wasting can lead to a weakened physical state that is detrimental to an individual's health, resulting in increased susceptibility to infection, poor performance status and susceptibility to injury.

SUMMARY OF THE INVENTION

[00015] The present invention relates to androgen receptor targeting agents (ARTA), which contain a haloacetamide or azide moiety and are alkylating agents. These agents either alone or in a composition, are useful for a) male contraception; b) treatment of a variety of hormone-related conditions, for example conditions associated with Androgen Decline in Aging Male (ADAM), such as fatigue, depression, decreased libido, sexual dysfunction, erectile dysfunction, hypogonadism, osteoporosis, hair loss, anemia, obesity, sarcopenia, osteopenia, osteoporosis, benign prostate hyperplasia, alterations in mood and cognition and prostate cancer; c) treatment of conditions associated with Androgen Decline in Female (ADIF), such as sexual dysfunction, decreased sexual libido, hypogonadism, sarcopenia, osteopenia, osteoporosis, alterations in cognition and mood, depression, anemia, hair loss, obesity, endometriosis, breast cancer, uterine cancer and ovarian cancer; d) treatment and/or prevention of acute and/or chronic muscular wasting conditions; e) preventing and/or treating dry eye conditions; f) oral androgen replacement therapy; g) decreasing the incidence of, halting or causing a regression of cancer cells; and/or h) inducing apoptosis in a cancer cell; and/or i) inducing cell cycle arrest; and/or j) inhibiting and/or suppressing cellular proliferation.

[00016] In one embodiment, the present invention provides a selective androgen receptor modulator (SARM) compound represented by the structure of formula I:



I

X is a bond, O, CH_2, NH, S, Se, PR, NO or NR;

G is O or S;

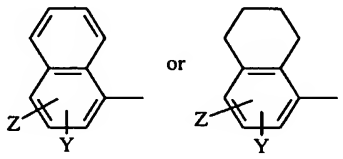
T is OH, OR, -$NHCOCH_3$, or NHCOR;

R is alkyl, haloalkyl, dihaloalkyl, trihaloalkyl, CH_2F, CHF_2, CF_3, CF_2CF_3, aryl, phenyl, halogen, alkenyl or OH;

R_1 is CH_3, CH_2F, CHF_2, CF_3, CH_2CH_3, or CF_2CF_3;

R_2 is F, Cl, Br, I, CH_3, CF_3, OH, CN, NO_2, $NHCOCH_3$, $NHCOCF_3$, NHCOR, alkyl, arylalkyl, OR, NH_2, NHR, NR_2, SR;

R_3 is F, Cl, Br, I, CN, NO_2, COR, COOH, CONHR, CF_3, SnR_3, or R_3 together with the benzene ring to which it is attached forms a fused ring system represented by the structure:



Z is NO_2, CN, COR, COOH, or CONHR;

Y is CF_3, F, Br, Cl, I, CN, or SnR_3;

Q is N_3 or $NHCOCH_2Hal$;

Hal is halogen;

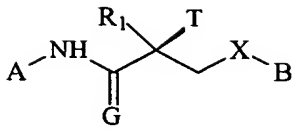
n is an integer of 1-4; and

m is an integer of 1-3.

[00017] In another embodiment, the present invention provides an analog, derivative, isomer, metabolite, pharmaceutically acceptable salt, pharmaceutical product, hydrate or N-oxide of the compound of formula I, or any combination thereof.

[00018] In one embodiment, G in compound I is O. In another embodiment, X in compound I is O. In another embodiment, T in compound I is OH. In another embodiment, R_1 in compound I is CH_3. In another embodiment, Z in compound I is NO_2. In another embodiment, Z in compound I is CN. In another embodiment, Y in compound I is CF_3. In another embodiment, Q in compound I is $NHCOCH_2Cl$. In another embodiment, Q in compound I is $NHCOCH_2Br$. In another embodiment, Q in compound I is N_3. In another embodiment, Q in compound I is in the para position. In another embodiment, Z in compound I is in the para position. In another embodiment, Y in compound I is in the meta position.

[00019] In another embodiment, the present invention provides a selective androgen receptor modulator (SARM) compound represented by the structure of formula II:



II

wherein X is a bond, O, CH_2, NH, S, Se, PR, NO or NR;

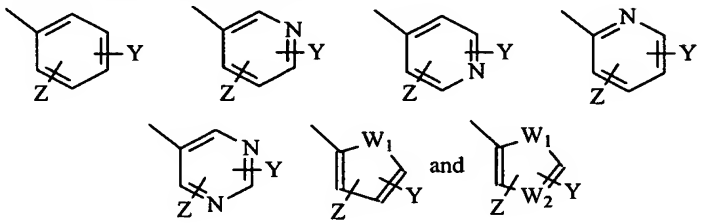
G is O or S;

R_1 is CH_3, CH_2F, CHF_2, CF_3, CH_2CH_3, or CF_2CF_3;

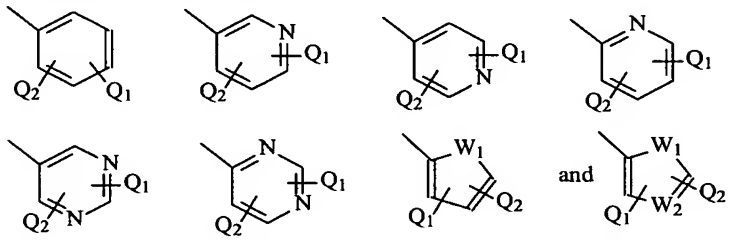
T is OH, OR, -$NHCOCH_3$, or NHCOR;

R is alkyl, haloalkyl, dihaloalkyl, trihaloalkyl, CH_2F, CHF_2, CF_3, CF_2CF_3, aryl, phenyl, halogen, alkenyl or OH;

A is a ring selected from:



B is a ring selected from:



wherein A and B cannot simultaneously be a benzene ring;

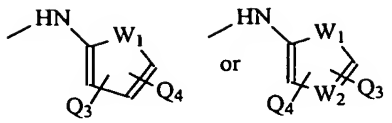
Z is NO_2, CN, COOH, COR, NHCOR or CONHR;

Y is CF_3, F, I, Br, Cl, CN CR_3 or SnR_3;

Q_1 is N_3 or $NHCOCH_2Hal$;

Hal is halogen;

Q_2 is a hydrogen, alkyl, halogen, CF_3, CN CR_3, SnR_3, NR_2, $NHCOCH_3$, $NHCOCF_3$, NHCOR, NHCONHR, NHCOOR, OCONHR, CONHR, $NHCSCH_3$, $NHCSCF_3$, NHCSR $NHSO_2CH_3$, $NHSO_2R$, OR, COR, OCOR, OSO_2R, SO_2R, SR,



Q_3 and Q_4 are independently of each other a hydrogen, alkyl, halogen, CF_3, CN CR_3, SnR_3, NR_2, $NHCOCH_3$, $NHCOCF_3$, NHCOR, NHCONHR, NHCOOR, OCONHR, CONHR, $NHCSCH_3$, $NHCSCF_3$, NHCSR $NHSO_2CH_3$, $NHSO_2R$, OR, COR, OCOR, OSO_2R, SO_2R or SR;

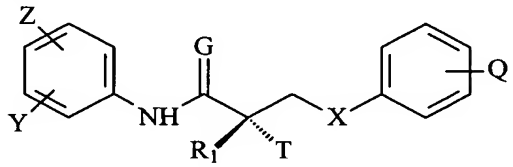
W_1 is O, NH, NR, NO or S; and

W_2 is N or NO.

[00020] In another embodiment, the present invention provides an analog, derivative, isomer, metabolite, pharmaceutically acceptable salt, pharmaceutical product, hydrate or N-oxide of the compound of formula II, or any combination thereof.

[00021] In one embodiment, G in compound II is O. In another embodiment, X in compound II is O. In another embodiment, T in compound II is OH. In another embodiment, R_1 in compound II is CH_3. In another embodiment, Z in compound II is NO_2. In another embodiment, Z in compound II is CN. In another embodiment, Y in compound II is CF_3. . In another embodiment, Q_1 in compound II is $NHCOCH_2Cl$. In another embodiment, Q_1 in compound II is $NHCOCH_2Br$. In another embodiment, Q_1 in compound II is N_3. In another embodiment, Q_1 in compound II is in the para position. In another embodiment, Z in compound II is in the para position. In another embodiment, Y in compound II is in the meta position.

[00022] In another embodiment, the present invention provides a selective androgen receptor modulator (SARM) compound represented by the structure of formula III:



III

wherein X is a bond, O, CH_2, NH, S, Se, PR, NO or NR;

G is O or S;

T is OH, OR, -$NHCOCH_3$, or NHCOR

Z is NO_2, CN, COOH, COR, NHCOR or CONHR;

Y is CF_3, F, I, Br, Cl, CN, CR_3 or SnR_3;

Q is N_3 or $NHCOCH_2Hal$;

Hal is halogen;

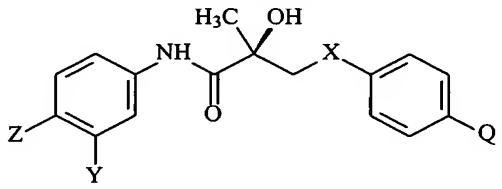
R is alkyl, haloalkyl, dihaloalkyl, trihaloalkyl, CH_2F, CHF_2, CF_3, CF_2CF_3, aryl, phenyl, halogen, alkenyl or OH; and

R_1 is CH_3, CH_2F, CHF_2, CF_3, CH_2CH_3, or CF_2CF_3.

[00023] In another embodiment, the present invention provides an analog, derivative, isomer, metabolite, pharmaceutically acceptable salt, pharmaceutical product, hydrate or N-oxide of the compound of formula III, or any combination thereof.

[00024] In one embodiment, G in compound III is O. In another embodiment, X in compound III is O. In another embodiment, T in compound III is OH. In another embodiment, R_1 in compound III is CH_3. In another embodiment, Z in compound III is NO_2. In another embodiment, Z in compound III is CN. In another embodiment, Y in compound III is CF_3. In another embodiment, Q in compound III is $NHCOCH_2Cl$. In another embodiment, Q in compound III is $NHCOCH_2Br$. In another embodiment, Q in compound III is N_3. In another embodiment, Q in compound III is in the para position. In another embodiment, Z in compound III is in the para position. In another embodiment, Y in compound III is in the meta position. In another embodiment, G in compound III is O, T is OH, R_1 is CH_3, X is O, Z is NO_2, Y is CF_3, and Q is NCS.

[00025] In another embodiment, the present invention provides a selective androgen receptor modulator (SARM) compound represented by the structure of formula IV:



IV

wherein X is a bond, O, CH_2, NH, S, Se, PR, NO or NR;

Z is NO_2, CN, COOH, COR, NHCOR or CONHR;

Y is CF_3, F, I, Br, Cl, CN, CR_3 or SnR_3;

Q is N_3 or $NHCOCH_2Hal$;

Hal is halogen; and

R is alkyl, haloalkyl, dihaloalkyl, trihaloalkyl, CH_2F, CHF_2, CF_3, CF_2CF_3, aryl, phenyl, halogen, alkenyl or OH.

[00026] In another embodiment, the present invention provides an analog, derivative, isomer, metabolite, pharmaceutically acceptable salt, pharmaceutical product, hydrate or N-oxide of the compound of formula IV, or any combination thereof.

[00027] In one embodiment, X in compound IV is O. In another embodiment, Z in compound IV is NO_2. In another embodiment, Z in compound IV is CN. In another embodiment, Y in compound IV is CF_3. In another embodiment, Q in compound IV is $NHCOCH_2Cl$. In another embodiment, Q in compound IV is $NHCOCH_2Br$. In another embodiment, Q in compound IV is N_3.

[00028] In one embodiment, the SARM compound of any of formulas I-IV is an alkylating agent. In another embodiment, the SARM compound of any of formulas I-IV is an androgen receptor agonist. In another embodiment, the SARM compound of any of formulas I-IV is an androgen receptor antagonist.

[00029] In one embodiment, the present invention provides a composition comprising the selective androgen receptor modulator compound of any of formulas I-IV and/or its analog, derivative, isomer, metabolite, pharmaceutically acceptable salt, pharmaceutical product, hydrate, N-oxide or any combination thereof.

[00030] In another embodiment, the present invention provides a pharmaceutical composition comprising the selective androgen receptor modulator compound of any of

formulas I-IV and/or its analog, derivative, isomer, metabolite, pharmaceutical product, hydrate, N-oxide or any combination thereof; and a suitable carrier or diluent.

[00031] In another embodiment, the present invention provides a method of suppressing spermatogenesis in a subject, comprising the step of administering to the subject the selective androgen receptor modulator compound of any of formulas I-IV and/or its analog, derivative, isomer, metabolite, pharmaceutically acceptable salt, pharmaceutical product, hydrate, N-oxide or any combination thereof, in an amount effective to suppress sperm production.

[00032] In another embodiment, the present invention provides a method of contraception in a male subject, comprising the step of administering to the subject the selective androgen receptor modulator compound of any of formulas I-IV and/or its analog, derivative, isomer, metabolite, pharmaceutically acceptable salt, pharmaceutical product, hydrate, N-oxide or any combination thereof, in an amount effective to suppress sperm production in the subject, thereby effecting contraception in the subject.

[00033] In another embodiment, the present invention further provides a method of hormone therapy, comprising the step of administering to the subject the selective androgen receptor modulator compound of any of any of formulas I-IV and/or its analog, derivative, isomer, metabolite, pharmaceutically acceptable salt, pharmaceutical product, hydrate, N-oxide or any combination thereof, in an amount effective to bind the selective androgen receptor modulator compound to the androgen receptor and effect a change in an androgen-dependent condition.

[00034] In another embodiment, the present invention provides a method of hormone replacement therapy comprising the step of administering to the subject the selective androgen receptor modulator compound of any of formulas I-IV and/or its analog, derivative, isomer, metabolite, pharmaceutically acceptable salt, pharmaceutical product, hydrate, N-oxide or any combination thereof, in an amount effective to effect a change in an androgen-dependent condition.

[00035] In another embodiment, the present invention further provides a method of treating a subject having a hormone related condition, comprising the step of administering to the subject the selective androgen receptor modulator compound of any of any of formulas I-IV and/or its analog, derivative, isomer, metabolite, pharmaceutically acceptable salt, pharmaceutical product, hydrate, N-oxide or any combination thereof, in an amount effective to bind the selective androgen receptor modulator compound to the androgen receptor and effect a change in an androgen-dependent condition.

[00036] In another embodiment, the present invention further provides a method of treating a subject suffering from prostate cancer, comprising the step of administering to the subject the selective androgen receptor modulator compound of any of formulas I-IV and/or its analog, derivative, isomer, metabolite, pharmaceutically acceptable salt, pharmaceutical product, hydrate, N-oxide or any combination thereof, in an amount effective to treat prostate cancer in the subject.

[00037] In another embodiment, the present invention provides a method of preventing prostate cancer in a subject, comprising the step of administering to the subject the selective androgen receptor modulator compound of formulas I-IV and/or its analog, derivative, isomer, metabolite, pharmaceutically acceptable salt, pharmaceutical product, hydrate, N-oxide or any combination thereof, in an amount effective to prevent prostate cancer in the subject.

[00038] In another embodiment, the present invention further provides a method of delaying the progression of prostate cancer in a subject suffering from prostate cancer, comprising the step of administering to the subject the selective androgen receptor modulator compound of any of any of formulas I-IV and/or its analog, derivative, isomer, metabolite, pharmaceutically acceptable salt, pharmaceutical product, hydrate, N-oxide or any combination thereof, in an amount effective to delay the progression of prostate cancer in the subject.

[00039] In another embodiment, the present invention further provides a method of preventing the recurrence of prostate cancer in a subject suffering from prostate cancer, comprising the step of administering to the subject the selective androgen receptor modulator compound of any of any of formulas I-IV and/or its analog, derivative, isomer, metabolite, pharmaceutically acceptable salt, pharmaceutical product, hydrate, N-oxide or any combination thereof, in an amount effective to prevent the recurrence of prostate cancer in the subject.

[00040] In another embodiment, the present invention provides a method of treating the recurrence of prostate cancer in a subject suffering from prostate cancer, comprising the step of administering to the subject the selective androgen receptor modulator compound of any of any of formulas I-IV and/or its analog, derivative, isomer, metabolite, pharmaceutically acceptable salt, pharmaceutical product, hydrate, N-oxide or any combination thereof, in an amount effective to treat the recurrence of prostate cancer in the subject.

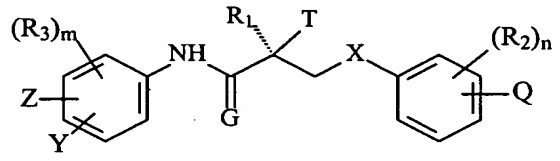
[00041] In another embodiment, the present invention provides a method of treating a dry eye condition in a subject suffering from dry eyes, comprising the step of administering to said subject the selective androgen receptor modulator compound of formulas I-IV and/or its analog, derivative, isomer, metabolite, pharmaceutically acceptable salt, pharmaceutical product, hydrate or N-oxide or any combination thereof, in an amount effective to treat dry eyes in the subject.

[00042] In another embodiment, the present invention provides a method of preventing a dry eye condition in a subject, comprising the step of administering to said subject the selective androgen receptor modulator compound of formulas I-IV and/or its analog, derivative, isomer, metabolite, pharmaceutically acceptable salt, pharmaceutical product, hydrate or N-oxide or any combination thereof, in an amount effective to prevent dry eyes in the subject.

[00043] In another embodiment, the present invention provides a method of inducing apoptosis in a prostate cancer cell, comprising the step of contacting the cell with the

selective androgen receptor modulator compound of any of any of formulas I-IV and/or its analog, derivative, isomer, metabolite, pharmaceutically acceptable salt, pharmaceutical product, hydrate, N-oxide or any combination thereof, in an amount effective to induce apoptosis in the cancer cell.

[00044] In another embodiment, the present invention provides process for preparing a selective androgen receptor modulator (SARM) compound represented by the structure of formula I:



I

wherein X is a O, NH, S, Se, PR, or NR;

G is O or S;

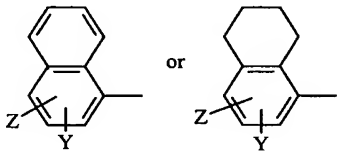
T is OH, OR, -$NHCOCH_3$, or NHCOR;

R is alkyl, haloalkyl, dihaloalkyl, trihaloalkyl, CH_2F, CHF_2, CF_3, CF_2CF_3, aryl, phenyl, halogen, alkenyl or OH;

R_1 is CH_3, CH_2F, CHF_2, CF_3, CH_2CH_3, or CF_2CF_3;

R_2 is F, Cl, Br, I, CH_3, CF_3, OH, CN, NO_2, $NHCOCH_3$, $NHCOCF_3$, NHCOR, alkyl, arylalkyl, OR, NH_2, NHR, NR_2, SR;

R_3 is F, Cl, Br, I, CN, NO_2, COR, COOH, CONHR, CF_3, SnR_3, or R_3 together with the benzene ring to which it is attached forms a fused ring system represented by the structure:



Z is NO_2, CN, COR, COOH, or CONHR;

Y is CF_3, F, Br, Cl, I, CN, or SnR_3;

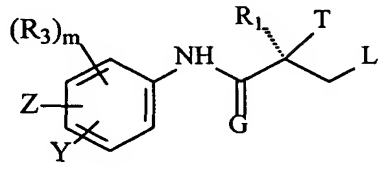
Q is N_3 or $NHCOCH_2Hal$;

Hal is halogen; and

n is an integer of 1-4; and

m is an integer of 1-3;

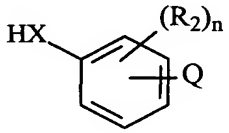
the process comprising the step of coupling a compound of formula VIII:



VIII

wherein Z, Y, G, R_1, T, R_3 and m are as defined above and L is a leaving group,

with a compound of formula IX:



IX

wherein Q, X R_2 and n are as defined above.

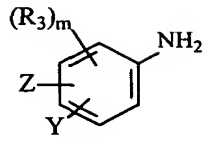
[00045] In one embodiment, the coupling step is carried out in the presence of a base. In another embodiment, the leaving group L is Br. In another embodiment, the compound of formula VIII is prepared by

a. preparing a compound of formula X by ring opening of a cyclic compound of formula XI

XI X

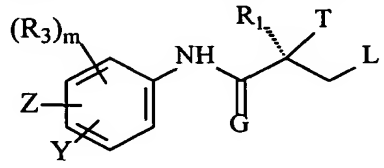
wherein L, R_1, G and T are as defined above, and T_1 is O or NH; and

b. reacting an amine of formula XII:



XII

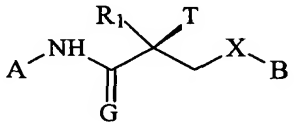
wherein Z, Y, R_3 and m are as defined above, with the compound of formula X, in the presence of a coupling reagent, to produce the compound of formula VIII.



VIII

[00046] In one embodiment, step (a) is carried out in the presence of HBr. In another embodiment, the process further comprises the step of converting the selective androgen receptor modulator (SARM) compound to its analog, isomer, metabolite, derivative, pharmaceutically acceptable salt, pharmaceutical product, N-oxide, hydrate or any combination thereof.

[00047] In another embodiment, the present invention provides process for preparing a selective androgen receptor modulator (SARM) compound represented by the structure of formula II:



II

wherein X is O, NH, S, Se, PR, or NR;

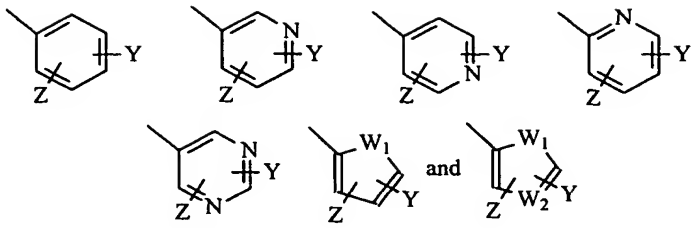
G is O or S;

R_1 is CH_3, CH_2F, CHF_2, CF_3, CH_2CH_3, or CF_2CF_3;

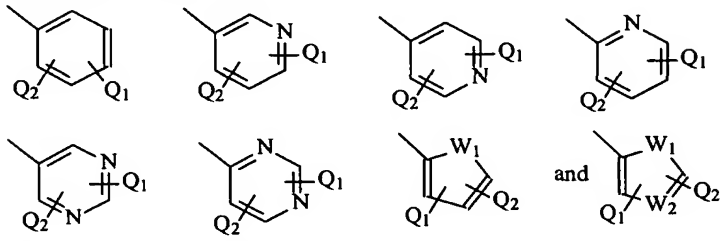
T is OH, OR, -$NHCOCH_3$, or NHCOR;

R is alkyl, haloalkyl, dihaloalkyl, trihaloalkyl, CH_2F, CHF_2, CF_3, CF_2CF_3, aryl, phenyl, halogen, alkenyl or OH;

A is a ring selected from:



B is a ring selected from:



wherein A and B cannot simultaneously be a benzene ring;

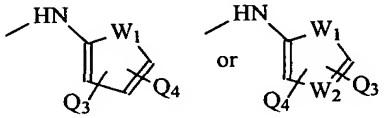
Z is NO_2, CN, COOH, COR, NHCOR or CONHR;

Y is CF_3, F, I, Br, Cl, CN CR_3 or SnR_3;

Q_1 is N_3 or $NHCOCH_2Hal$;

Hal is halogen; and

Q_2 is a hydrogen, alkyl, halogen, CF_3, CN CR_3, SnR_3, NR_2, $NHCOCH_3$, $NHCOCF_3$, NHCOR, NHCONHR, NHCOOR, OCONHR, CONHR, $NHCSCH_3$, $NHCSCF_3$, NHCSR $NHSO_2CH_3$, $NHSO_2R$, OR, COR, OCOR, OSO_2R, SO_2R, SR,

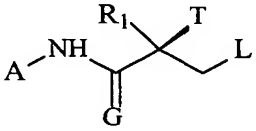


Q_3 and Q_4 are independently of each other a hydrogen, alkyl, halogen, CF_3, CN CR_3, SnR_3, NR_2, $NHCOCH_3$, $NHCOCF_3$, NHCOR, NHCONHR, NHCOOR, OCONHR, CONHR, $NHCSCH_3$, $NHCSCF_3$, NHCSR $NHSO_2CH_3$, $NHSO_2R$, OR, COR, OCOR, OSO_2R, SO_2R or SR;

W_1 is O, NH, NR, NO or S; and

W_2 is N or NO;

the process comprising the step of coupling a compound of formula XIII:



XIII

wherein A, G, R_1 and T are as defined above and L is a leaving group, with a compound of formula HX-B wherein B and X are as defined above.

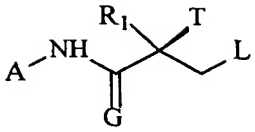
[00048] In one embodiment, the coupling step is carried out in the presence of a base. In another embodiment, the leaving group L is Br. In another embodiment, the compound of formula XIII is prepared by

a. preparing a compound formula X by ring opening of a cyclic compound of formula XI

XI X

wherein L, R_1, G and T are as defined above, and T_1 is O or NH; and

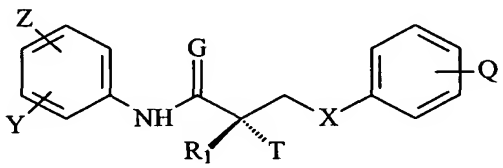
b. reacting an amine of formula A-NH_2 wherein A is as defined above, with the compound of formula X in the presence of a coupling reagent, to produce the amide of formula XIII.



XIII

[00049] In one embodiment, step (a) is carried out in the presence of HBr. In another embodiment, the process further comprises the step of converting the selective androgen receptor modulator (SARM) compound to its analog, isomer, metabolite, derivative, pharmaceutically acceptable salt, pharmaceutical product, N-oxide, hydrate or any combination thereof.

[00050] In another embodiment, the present invention provides process for preparing a selective androgen receptor modulator (SARM) compound represented by the structure of formula III:



III

wherein X is O, NH, S, Se, PR or NR;

G is O or S;

T is OH, OR, -$NHCOCH_3$, or NHCOR

Z is NO_2, CN, COOH, COR, NHCOR or CONHR;

Y is CF_3, F, I, Br, Cl, CN, CR_3 or SnR_3;

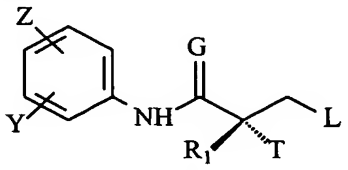
Q is N_3 or $NHCOCH_2Hal$;

Hal is halogen; and

R is alkyl, haloalkyl, dihaloalkyl, trihaloalkyl, CH_2F, CHF_2, CF_3, CF_2CF_3, aryl, phenyl, halogen, alkenyl or OH; and

R_1 is CH_3, CH_2F, CHF_2, CF_3, CH_2CH_3, or CF_2CF_3;

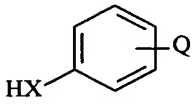
the process comprising the step of coupling a compound of formula XIV:



XIV

wherein Z, Y, G R_1 and T are as defined above and L is a leaving group,

with a compound of formula XV:



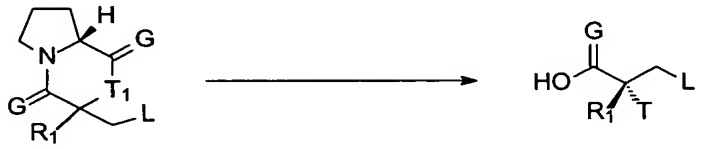
XV

wherein Q and X are as defined above.

[00051] In one embodiment, the coupling step is carried out in the presence of a base. In another embodiment, the leaving group L is Br. In another embodiment, the compound of formula XIV is prepared by

a. preparing a compound formula X by ring opening of a cyclic compound

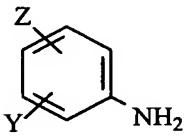
of formula XI



XI X

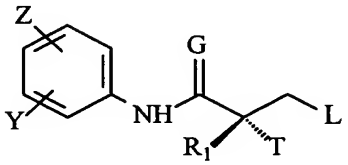
wherein L, R_1, and T are as defined above, G is O and T_1 is O or NH; and

b. reacting an amine of formula XVI



XVI

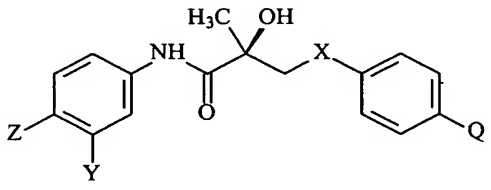
with the compound of formula X in the presence of a coupling reagent, to produce the compound of formula XIV.



XIV

[00052] In one embodiment, step (a) is carried out in the presence of HBr. In another embodiment, the process further comprises the step of converting the selective androgen receptor modulator (SARM) compound to its analog, isomer, metabolite, derivative, pharmaceutically acceptable salt, pharmaceutical product, N-oxide, hydrate or any combination thereof.

[00053] In another embodiment, the present invention provides process for preparing a selective androgen receptor modulator (SARM) compound represented by the structure of formula IV:



IV

wherein X is O, NH, S, Se, PR, or NR;

Z is NO_2, CN, COOH, COR, NHCOR or CONHR;

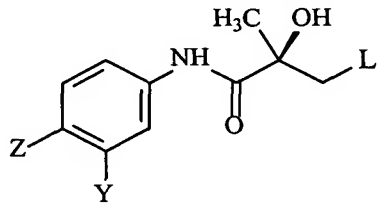
Y is CF_3, F, I, Br, Cl, CN, CR_3 or SnR_3;

Q is N_3 or $NHCOCH_2Hal$;

Hal is halogen; and

R is alkyl, haloalkyl, dihaloalkyl, trihaloalkyl, CH_2F, CHF_2, CF_3, CF_2CF_3, aryl, phenyl, halogen, alkenyl or OH;

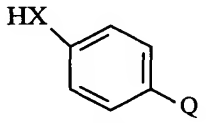
the process comprising the step of coupling an amide of formula XVII:



XVII

wherein Z and Y are as defined above and L is a leaving group,

with a compound of formula XVIII:



XVIII

wherein Q and X R_2 are as defined above.

[00054] In one embodiment, the coupling step is carried out in the presence of a base. In another embodiment, the leaving group L is Br. In another embodiment, the compound of formula XVII is prepared by

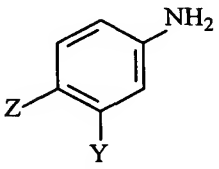
a. preparing a compound formula X by

ring opening of a cyclic compound of formula XI

XI X

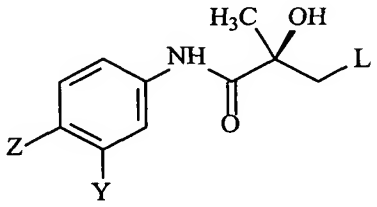
wherein L, R_1, and T are as defined above, G is O and T_1 is O or NH; and

b. reacting an amine of formula XVIX



XVIX

with the compound of formula X in the presence of a coupling reagent, to produce the compound of formula XVII.



XVII

In one embodiment, step (a) is carried out in the presence of HBr. In another embodiment, the process further comprises the step of purifying the SARM compound using a mixture of ethanol and water. In another embodiment, the process further comprises the step of converting the selective androgen receptor modulator (SARM)

compound to its analog, isomer, metabolite, derivative, pharmaceutically acceptable salt, pharmaceutical product, N-oxide, hydrate or any combination thereof.

[00055] The novel selective androgen receptor modulator compounds of the present invention, either alone or as a pharmaceutical composition, are useful for a) male contraception; b) treatment of a variety of hormone-related conditions, for example conditions associated with ADAM, such as fatigue, depression, decreased libido, sexual dysfunction, erectile dysfunction, hypogonadism, osteoporosis, hair loss, obesity, sarcopenia, osteopenia, benign prostate hyperplasia, and alterations in mood and cognition; c) treatment of conditions associated with ADIF, such as sexual dysfunction, decreased sexual libido, hypogonadism, sarcopenia, osteopenia, osteoporosis, alterations in cognition and mood, depression, anemia, hair loss, obesity, endometriosis, breast cancer, uterine cancer and ovarian cancer; d) treatment and/or prevention of acute and/or chronic muscular wasting conditions; e) preventing and/or treating dry eye conditions; f) oral androgen replacement therapy; g) decreasing the incidence of, halting or causing a regression of prostate cancer; and/or h) inducing apoptosis in a cancer cell.

[00056] The selective androgen receptor modulator compounds of the present invention offer a significant advance over steroidal androgen treatment since treatment with the compounds of the present invention will not be accompanied by serious side effects, inconvenient modes of administration, or high costs and still have the advantages of oral bioavailability, lack of cross-reactivity with other steroid receptors, and long biological half-lives.

BRIEF DESCRIPTION OF THE DRAWINGS

[00057] The present invention will be understood and appreciated more fully from the following detailed description taken in conjunction with the appended drawings in which:

FIG 1A: Cytotoxicity of compound 1 (bromoacetemido substituted) in different cell lines.

FIG 1B: Cytotoxicity of compound 2 (chlorocetemido substituted) in different cell lines.

FIG 1C: Cytotoxicity of compound S-NTBA in different cell lines.

FIG 2A: Growth Curve: Effect of compound 1 (bromoacetamido substituted) on growth of different cell lines.

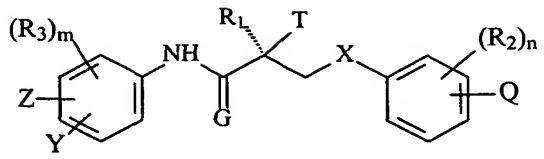
FIG 2B: Growth Curve: Effect of compound 2 (chloroacetamido substituted) on growth of different cell lines.

FIG 3A, B: Tunnel Assay: Top panel: LNCaP cells exposed to Compound 1 for 24 hours. Bottom Panel: 0.1% vehicle control.

DETAILED DESCRIPTION OF THE INVENTION

[00058] The present invention relates to androgen receptor targeting agents (ARTA), which contain a haloacetamide or azide moiety and are alkylating agents. These agents either alone or in a composition, are useful for a) male contraception; b) treatment of a variety of hormone-related conditions, for example conditions associated with Androgen Decline in Aging Male (ADAM), such as fatigue, depression, decreased libido, sexual dysfunction, erectile dysfunction, hypogonadism, osteoporosis, hair loss, anemia, obesity, sarcopenia, osteopenia, osteoporosis, benign prostate hyperplasia, alterations in mood and cognition and prostate cancer; c) treatment of conditions associated with Androgen Decline in Female (ADIF), such as sexual dysfunction, decreased sexual libido, hypogonadism, sarcopenia, osteopenia, osteoporosis, alterations in cognition and mood, depression, anemia, hair loss, obesity, endometriosis, breast cancer, uterine cancer and ovarian cancer; d) treatment and/or prevention of acute and/or chronic muscular wasting conditions; e) preventing and/or treating dry eye conditions; f) oral androgen replacement therapy; g) decreasing the incidence of, halting or causing a regression of cancer cells; and/or h) inducing apoptosis in a cancer cell; and/or i) inducing cell cycle arrest; and/or j) inhibiting and/or suppressing cellular proliferation.

[00059] In one embodiment, the present invention provides a selective androgen receptor modulator (SARM) compound represented by the structure of formula I:



I

X is a bond, O, CH_2, NH, S, Se, PR, NO or NR;

G is O or S;

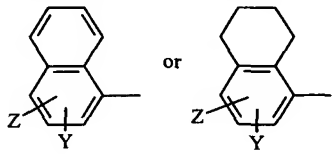
T is OH, OR, -$NHCOCH_3$, or NHCOR;

R is alkyl, haloalkyl, dihaloalkyl, trihaloalkyl, CH_2F, CHF_2, CF_3, CF_2CF_3, aryl, phenyl, halogen, alkenyl or OH;

R_1 is CH_3, CH_2F, CHF_2, CF_3, CH_2CH_3, or CF_2CF_3;

R_2 is F, Cl, Br, I, CH_3, CF_3, OH, CN, NO_2, $NHCOCH_3$, $NHCOCF_3$, NHCOR, alkyl, arylalkyl, OR, NH_2, NHR, NR_2, SR;

R_3 is F, Cl, Br, I, CN, NO_2, COR, COOH, CONHR, CF_3, SnR_3, or R_3 together with the benzene ring to which it is attached forms a fused ring system represented by the structure:



Z is NO_2, CN, COR, COOH, or CONHR;

Y is CF_3, F, Br, Cl, I, CN, or SnR_3;

Q is N_3 or $NHCOCH_2Hal$;

Hal is halogen;

n is an integer of 1-4; and

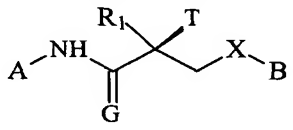
m is an integer of 1-3.

[00060] In one embodiment, this invention provides an analog of the compound of formula I. In another embodiment, this invention provides a derivative of the compound of formula I. In another embodiment, this invention provides an isomer of the compound of formula I. In another embodiment, this invention provides a metabolite of the compound of formula I. In another embodiment, this invention provides a pharmaceutically acceptable salt of the compound of formula I. In another embodiment,

this invention provides a pharmaceutical product of the compound of formula I. In another embodiment, this invention provides a hydrate of the compound of formula I. In another embodiment, this invention provides an N-oxide of the compound of formula I. In another embodiment, this invention provides a combination of any of an analog, derivative, metabolite, isomer, pharmaceutically acceptable salt, pharmaceutical product, hydrate or N-oxide of the compound of formula I.

[00061] In one embodiment, G in compound I is O. In another embodiment, X in compound I is O. In another embodiment, T in compound I is OH. In another embodiment, R_1 in compound I is CH_3. In another embodiment, Z in compound I is NO_2. In another embodiment, Z in compound I is CN. In another embodiment, Y in compound I is CF_3. In another embodiment, Q in compound I is $NHCOCH_2Cl$. In another embodiment, Q in compound I is $NHCOCH_2Br$. In another embodiment, Q in compound I is N_3. In another embodiment, Q in compound I is in the para position. In another embodiment, Z in compound I is in the para position. In another embodiment, Y in compound I is in the meta position.

[00062] In another embodiment, the present invention provides a selective androgen receptor modulator (SARM) compound represented by the structure of formula II:



II

wherein X is a bond, O, CH_2, NH, S, Se, PR, NO or NR;

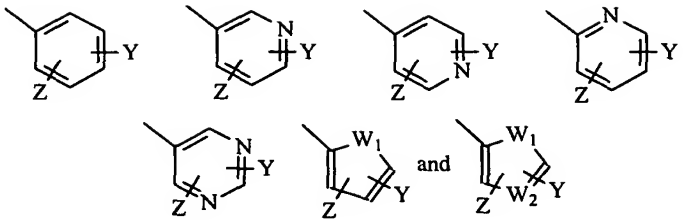
G is O or S;

R_1 is CH_3, CH_2F, CHF_2, CF_3, CH_2CH_3, or CF_2CF_3;

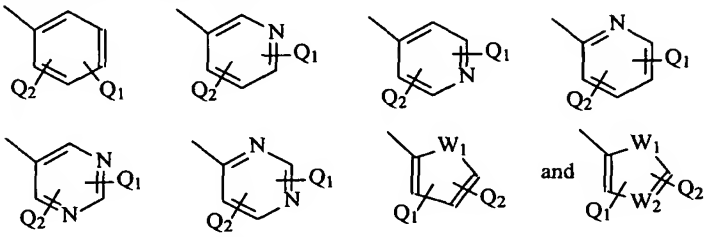
T is OH, OR, -$NHCOCH_3$, or NHCOR;

R is alkyl, haloalkyl, dihaloalkyl, trihaloalkyl, CH_2F, CHF_2, CF_3, CF_2CF_3, aryl, phenyl, halogen, alkenyl or OH;

A is a ring selected from:



B is a ring selected from:



wherein A and B cannot simultaneously be a benzene ring;

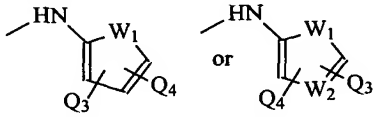
Z is NO_2, CN, COOH, COR, NHCOR or CONHR;

Y is CF_3, F, I, Br, Cl, CN CR_3 or SnR_3;

Q_1 is N_3 or $NHCOCH_2Hal$;

Hal is halogen;

Q_2 is a hydrogen, alkyl, halogen, CF_3, CN CR_3, SnR_3, NR_2, $NHCOCH_3$, $NHCOCF_3$, NHCOR, NHCONHR, NHCOOR, OCONHR, CONHR, $NHCSCH_3$, $NHCSCF_3$, NHCSR $NHSO_2CH_3$, $NHSO_2R$, OR, COR, OCOR, OSO_2R, SO_2R, SR,



Q_3 and Q_4 are independently of each other a hydrogen, alkyl, halogen, CF_3, CN CR_3, SnR_3, NR_2, $NHCOCH_3$, $NHCOCF_3$, NHCOR, NHCONHR, NHCOOR, OCONHR, CONHR, $NHCSCH_3$, $NHCSCF_3$, NHCSR $NHSO_2CH_3$, $NHSO_2R$, OR, COR, OCOR, OSO_2R, SO_2R or SR;

W_1 is O, NH, NR, NO or S; and

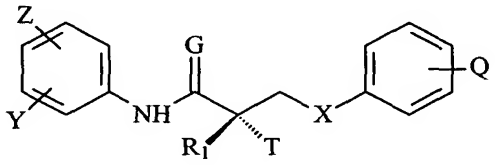
W_2 is N or NO.

[00063] In one embodiment, this invention provides an analog of the compound of formula II. In another embodiment, this invention provides a derivative of the compound

of formula II. In another embodiment, this invention provides an isomer of the compound of formula II. In another embodiment, this invention provides a metabolite of the compound of formula II. In another embodiment, this invention provides a pharmaceutically acceptable salt of the compound of formula II. In another embodiment, this invention provides a pharmaceutical product of the compound of formula II. In another embodiment, this invention provides a hydrate of the compound of formula II. In another embodiment, this invention provides an N-oxide of the compound of formula II. In another embodiment, this invention provides a combination of any of an analog, derivative, metabolite, isomer, pharmaceutically acceptable salt, pharmaceutical product, hydrate or N-oxide of the compound of formula II.

[00064] In one embodiment, G in compound II is O. In another embodiment, X in compound II is O. In another embodiment, T in compound II is OH. In another embodiment, R_1 in compound II is CH_3. In another embodiment, Z in compound II is NO_2. In another embodiment, Z in compound II is CN. In another embodiment, Y in compound II is CF_3. . In another embodiment, Q_1 in compound II is $NHCOCH_2Cl$. In another embodiment, Q_1 in compound II is $NHCOCH_2Br$. In another embodiment, Q_1 in compound II is N_3. In another embodiment, Q_1 in compound II is in the para position. In another embodiment, Z in compound II is in the para position. In another embodiment, Y in compound II is in the meta position.

[00065] In another embodiment, the present invention provides a selective androgen receptor modulator (SARM) compound represented by the structure of formula III:



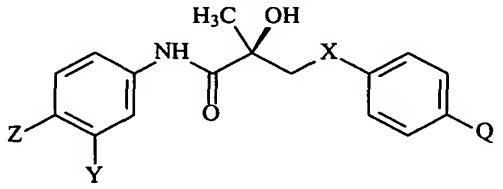
III

wherein X is a bond, O, CH_2, NH, S, Se, PR, NO or NR;
G is O or S;
T is OH, OR, -$NHCOCH_3$, or NHCOR
Z is NO_2, CN, COOH, COR, NHCOR or CONHR;
Y is CF_3, F, I, Br, Cl, CN, CR_3 or SnR_3;
Q is N_3 or $NHCOCH_2Hal$;
Hal is halogen;
R is alkyl, haloalkyl, dihaloalkyl, trihaloalkyl, CH_2F, CHF_2, CF_3, CF_2CF_3, aryl, phenyl, halogen, alkenyl or OH; and
R_1 is CH_3, CH_2F, CHF_2, CF_3, CH_2CH_3, or CF_2CF_3.

[00066] In one embodiment, G in compound III is O. In another embodiment, X in compound III is O. In another embodiment, T in compound III is OH. In another embodiment, R_1 in compound III is CH_3. In another embodiment, Z in compound III is NO_2. In another embodiment, Z in compound III is CN. In another embodiment, Y in compound III is CF_3. In another embodiment, Q in compound III is $NHCOCH_2Cl$. In another embodiment, Q in compound III is $NHCOCH_2Br$. In another embodiment, Q in compound III is N_3. In another embodiment, Q in compound III is in the para position. In another embodiment, Z in compound III is in the para position. In another embodiment, Y in compound III is in the meta position. In another embodiment, G in compound III is O, T is OH, R_1 is CH_3, X is O, Z is NO_2, Y is CF_3, and Q is NCS.

[00067] In one embodiment, G in compound III is O. In another embodiment, X in compound III is O. In another embodiment, T in compound III is OH. In another embodiment, R_1 in compound III is CH_3. In another embodiment, Z in compound III is NO_2. In another embodiment, Z in compound III is CN. In another embodiment, Y in compound III is CF_3. In another embodiment, Q in compound III is NCS. In another embodiment, Q in compound III is in the para position. In another embodiment, Z in compound III is in the para position. In another embodiment, Y in compound III is in the meta position. In another embodiment, G in compound III is O, T is OH, R_1 is CH_3, X is O, Z is NO_2, Y is CF_3, and Q is NCS.

[00068] In another embodiment, the present invention provides a selective androgen receptor modulator (SARM) compound represented by the structure of formula IV:



IV

wherein X is a bond, O, CH_2, NH, S, Se, PR, NO or NR;

Z is NO_2, CN, COOH, COR, NHCOR or CONHR;

Y is CF_3, F, I, Br, Cl, CN, CR_3 or SnR_3;

Q is N_3 or $NHCOCH_2Hal$;

Hal is halogen; and

R is alkyl, haloalkyl, dihaloalkyl, trihaloalkyl, CH_2F, CHF_2, CF_3, CF_2CF_3, aryl, phenyl, halogen, alkenyl or OH.

[00069] In one embodiment, this invention provides an analog of the compound of formula IV. In another embodiment, this invention provides a derivative of the compound of formula IV. In another embodiment, this invention provides an isomer of the compound of formula IV. In another embodiment, this invention provides a metabolite of the compound of formula IV. In another embodiment, this invention provides a pharmaceutically acceptable salt of the compound of formula IV. In another embodiment, this invention provides a pharmaceutical product of the compound of formula IV. In another embodiment, this invention provides a hydrate of the compound of formula IV. In another embodiment, this invention provides an N-oxide of the compound of formula IV. In another embodiment, this invention provides a combination of any of an analog, derivative, metabolite, isomer, pharmaceutically acceptable salt, pharmaceutical product, hydrate or N-oxide of the compound of formula IV.

[00070] In one embodiment, X in compound IV is O. In another embodiment, Z in compound IV is NO_2. In another embodiment, Z in compound IV is CN. In another embodiment, Y in compound IV is CF_3. In another embodiment, Q in compound IV is

$NHCOCH_2Cl$. In another embodiment, Q in compound IV is $NHCOCH_2Br$. In another embodiment, Q in compound IV is N_3.

[00071] The substituent R is defined herein as an alkyl, haloalkyl, dihaloalkyl, trihaloalkyl, CH_2F, CHF_2, CF_3, CF_2CF_3; aryl, phenyl, halogen, alkenyl, or hydroxyl (OH).

[00072] An "alkyl" group refers to a saturated aliphatic hydrocarbon, including straight-chain, branched-chain and cyclic alkyl groups. In one embodiment, the alkyl group has 1-12 carbons. In another embodiment, the alkyl group has 1-7 carbons. In another embodiment, the alkyl group has 1-6 carbons. In another embodiment, the alkyl group has 1-4 carbons. The alkyl group may be unsubstituted or substituted by one or more groups selected from halogen, hydroxy, alkoxy carbonyl, amido, alkylamido, dialkylamido, nitro, amino, alkylamino, dialkylamino, carboxyl, thio and thioalkyl.

[00073] A "haloalkyl" group refers to an alkyl group as defined above, which is substituted by one or more halogen atoms, e.g. by F, Cl, Br or I.

[00074] An "aryl" group refers to an aromatic group having at least one carbocyclic aromatic group or heterocyclic aromatic group, which may be unsubstituted or substituted by one or more groups selected from halogen, haloalkyl, hydroxy, alkoxy carbonyl, amido, alkylamido, dialkylamido, nitro, amino, alkylamino, dialkylamino, carboxy or thio or thioalkyl. Nonlimiting examples of aryl rings are phenyl, naphthyl, pyranyl, pyrrolyl, pyrazinyl, pyrimidinyl, pyrazolyl, pyridinyl, furanyl, thiophenyl, thiazolyl, imidazolyl, isoxazolyl, and the like.

[00075] A "hydroxyl" group refers to an OH group. An "alkenyl" group refers to a group having at least one carbon to carbon double bond. A halo group refers to F, Cl, Br or I.

[00076] An "arylalkyl" group refers to an alkyl bound to an aryl, wherein alkyl and aryl are as defined above. An example of an aralkyl group is a benzyl group.

[00077] As contemplated herein, the present invention relates to the use of a SARM compound and/or its analog, derivative, isomer, metabolite, pharmaceutically acceptable salt, pharmaceutical product, hydrate, N-oxide, or combinations thereof. In one embodiment, the invention relates to the use of an analog of the SARM compound. In another embodiment, the invention relates to the use of a derivative of the SARM compound. In another embodiment, the invention relates to the use of an isomer of the SARM compound. In another embodiment, the invention relates to the use of a metabolite of the SARM compound. In another embodiment, the invention relates to the use of a pharmaceutically acceptable salt of the SARM compound. In another embodiment, the invention relates to the use of a pharmaceutical product of the SARM compound. In another embodiment, the invention relates to the use of a hydrate of the SARM compound. In another embodiment, the invention relates to the use of an N-oxide of the SARM compound. In another embodiment, the invention relates to the use of any of a combination of an analog, derivative, isomer, metabolite, pharmaceutically acceptable salt, pharmaceutical product, hydrate, or N-oxide of the SARM compounds of the present invention.

[00078] As defined herein, the term "isomer" includes, but is not limited to, optical isomers and analogs, structural isomers and analogs, conformational isomers and analogs, and the like.

[00079] In one embodiment, this invention encompasses the use of various optical isomers of the SARM compound. It will be appreciated by those skilled in the art that the SARMs of the present invention contain at least one chiral center. Accordingly, the SARMs used in the methods of the present invention may exist in, and be isolated in, optically-active or racemic forms. Some compounds may also exhibit polymorphism. It is to be understood that the present invention encompasses any racemic, optically-active, polymorphic, or stereroisomeric form, or mixtures thereof, which form possesses properties useful in the treatment of androgen-related conditions described herein. In one embodiment, the SARMs are the pure (R)-isomers. In another embodiment, the SARMs are the pure (S)-isomers. In another embodiment, the SARMs are a mixture of

the (R) and the (S) isomers. In another embodiment, the SARMs are a racemic mixture comprising an equal amount of the (R) and the (S) isomers. It is well known in the art how to prepare optically-active forms (for example, by resolution of the racemic form by recrystallization techniques, by synthesis from optically-active starting materials, by chiral synthesis, or by chromatographic separation using a chiral stationary phase).

[00080] The invention includes pharmaceutically acceptable salts of amino-substituted compounds with organic and inorganic acids, for example, citric acid and hydrochloric acid. The invention also includes N-oxides of the amino substituents of the compounds described herein. Pharmaceutically acceptable salts can also be prepared from the phenolic compounds by treatment with inorganic bases, for example, sodium hydroxide. Also, esters of the phenolic compounds can be made with aliphatic and aromatic carboxylic acids, for example, acetic acid and benzoic acid esters.

[00081] This invention further includes derivatives of the SARM compounds. The term "derivatives" includes but is not limited to ether derivatives, acid derivatives, amide derivatives, ester derivatives and the like. In addition, this invention further includes hydrates of the SARM compounds. The term "hydrate" includes but is not limited to hemihydrate, monohydrate, dihydrate, trihydrate and the like.

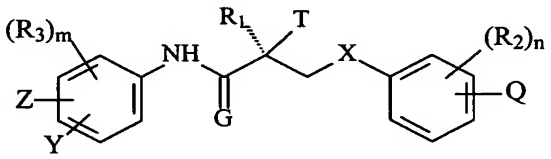
[00082] This invention further includes metabolites of the SARM compounds. The term "metabolite" means any substance produced from another substance by metabolism or a metabolic process.

[00083] This invention further includes pharmaceutical products of the SARM compounds. The term "pharmaceutical product" means a composition suitable for pharmaceutical use (pharmaceutical composition), as defined herein.

[00084] In another embodiment, the present invention provides process for preparing the selective androgen receptor modulator (SARM) compounds of the present invention.

[00085] The process of the present invention is suitable for large-scale preparation, since all of the steps give rise to highly pure compounds, thus avoiding complicated purification procedures which ultimately lower the yield. Thus the present invention provides methods for the synthesis of non-steroidal agonist compounds, that can be used for industrial large-scale synthesis, and that provide highly pure products in high yield.

[00086] Thus, in another embodiment, the present invention provides process for preparing a selective androgen receptor modulator (SARM) compound represented by the structure of formula I:



I

wherein X is a O, NH, S, Se, PR, or NR;

G is O or S;

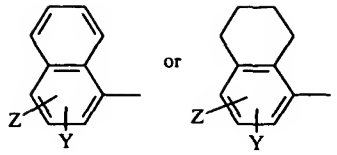
T is OH, OR, -$NHCOCH_3$, or NHCOR;

R is alkyl, haloalkyl, dihaloalkyl, trihaloalkyl, CH_2F, CHF_2, CF_3, CF_2CF_3, aryl, phenyl, halogen, alkenyl or OH;

R_1 is CH_3, CH_2F, CHF_2, CF_3, CH_2CH_3, or CF_2CF_3;

R_2 is F, Cl, Br, I, CH_3, CF_3, OH, CN, NO_2, $NHCOCH_3$, $NHCOCF_3$, NHCOR, alkyl, arylalkyl, OR, NH_2, NHR, NR_2, SR;

R_3 is F, Cl, Br, I, CN, NO_2, COR, COOH, CONHR, CF_3, SnR_3, or R_3 together with the benzene ring to which it is attached forms a fused ring system represented by the structure:



Z is NO_2, CN, COR, COOH, or CONHR;

Y is CF_3, F, Br, Cl, I, CN, or SnR_3;

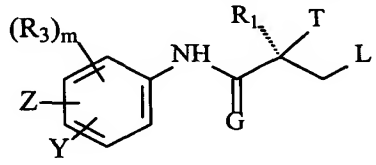
Q is N_3 or $NHCOCH_2Hal$;

Hal is halogen; and

n is an integer of 1-4; and

m is an integer of 1-3;

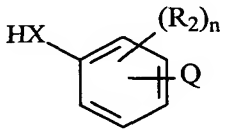
the process comprising the step of coupling a compound of formula VIII:



VIII

wherein Z, Y, G, R_1, T, R_3 and m are as defined above and L is a leaving group,

with a compound of formula IX:

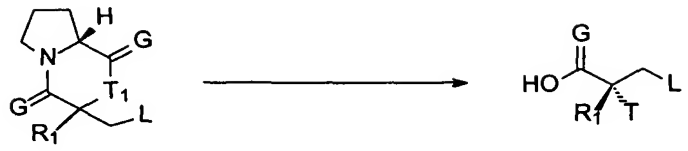


IX

wherein Q, X R_2 and n are as defined above.

[00087] In one embodiment, the coupling step is carried out in the presence of a base. In another embodiment, the leaving group L is Br. In another embodiment, the compound of formula VIII is prepared by

a. preparing a compound of formula X by ring opening of a cyclic compound of formula XI

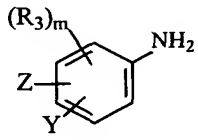


XI X

wherein L, R_1, G and T are as defined above, and T_1 is O or NH; and

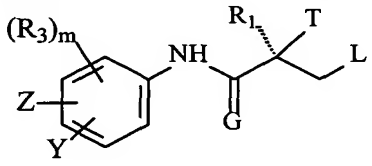
b. reacting an amine of formula

XII:



XII

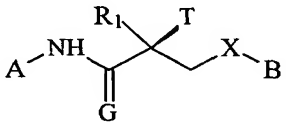
wherein Z, Y, R_3 and m are as defined above, with the compound of formula X, in the presence of a coupling reagent, to produce the compound of formula VIII.



VIII

[00088] In one embodiment, step (a) is carried out in the presence of HBr. In another embodiment, the process further comprises the step of converting the selective androgen receptor modulator (SARM) compound to its analog, isomer, metabolite, derivative, pharmaceutically acceptable salt, pharmaceutical product, N-oxide, hydrate or any combination thereof.

[00089] In another embodiment, the present invention provides process for preparing a selective androgen receptor modulator (SARM) compound represented by the structure of formula II:



II

wherein X is O, NH, S, Se, PR, or NR;

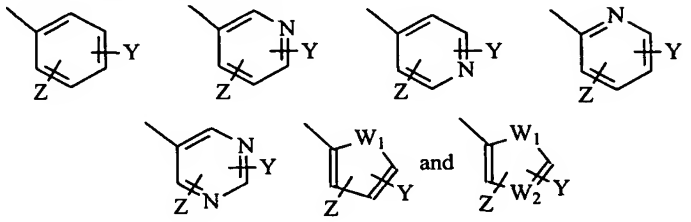
G is O or S;

R_1 is CH_3, CH_2F, CHF_2, CF_3, CH_2CH_3, or CF_2CF_3;

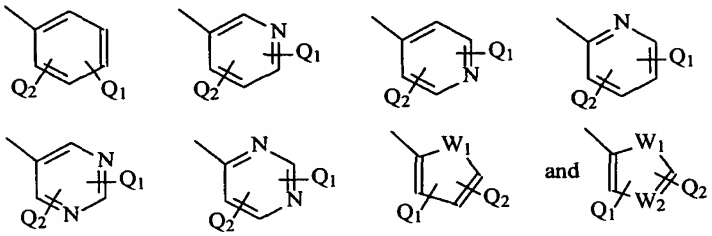
T is OH, OR, -$NHCOCH_3$, or NHCOR;

R is alkyl, haloalkyl, dihaloalkyl, trihaloalkyl, CH_2F, CHF_2, CF_3, CF_2CF_3, aryl, phenyl, halogen, alkenyl or OH;

A is a ring selected from:



B is a ring selected from:



wherein A and B cannot simultaneously be a benzene ring;

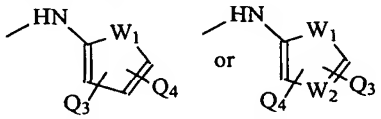
Z is NO_2, CN, COOH, COR, NHCOR or CONHR;

Y is CF_3, F, I, Br, Cl, CN CR_3 or SnR_3;

Q_1 is N_3 or $NHCOCH_2Hal$;

Hal is halogen; and

Q_2 is a hydrogen, alkyl, halogen, CF_3, CN CR_3, SnR_3, NR_2, $NHCOCH_3$, $NHCOCF_3$, NHCOR, NHCONHR, NHCOOR, OCONHR, CONHR, $NHCSCH_3$, $NHCSCF_3$, NHCSR $NHSO_2CH_3$, $NHSO_2R$, OR, COR, OCOR, OSO_2R, SO_2R, SR,



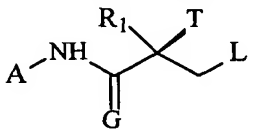
Q_3 and Q_4 are independently of each other a hydrogen, alkyl, halogen, CF_3, CN CR_3, SnR_3, NR_2, $NHCOCH_3$, $NHCOCF_3$, NHCOR,

NHCONHR, NHCOOR, OCONHR, CONHR, $NHCSCH_3$, $NHCSCF_3$, NHCSR $NHSO_2CH_3$, $NHSO_2R$, OR, COR, OCOR, OSO_2R, SO_2R or SR;

W_1 is O, NH, NR, NO or S; and

W_2 is N or NO;

the process comprising the step of coupling a compound of formula XIII:



XIII

wherein A, G, R_1 and T are as defined above and L is a leaving group,

with a compound of formula HX-B wherein B and X are as defined above.

[00090] In one embodiment, the coupling step is carried out in the presence of a base. In another embodiment, the leaving group L is Br. In another embodiment, the compound of formula XIII is prepared by

a. preparing a compound formula X by ring opening of a cyclic compound

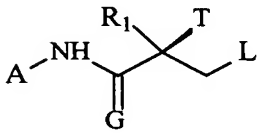
of formula XI

XI X

wherein L, R_1, G and T are as defined above, and T_1 is O or NH; and

b. reacting an amine of formula A-

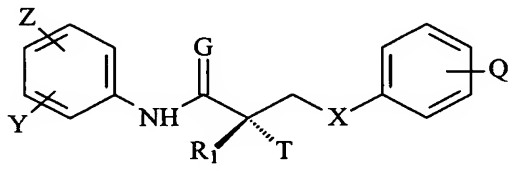
NH_2 wherein A is as defined above, with the compound of formula X in the presence of a coupling reagent, to produce the amide of formula XIII.



XIII

[00091] In one embodiment, step (a) is carried out in the presence of HBr. In another embodiment, the process further comprises the step of converting the selective androgen receptor modulator (SARM) compound to its analog, isomer, metabolite, derivative, pharmaceutically acceptable salt, pharmaceutical product, N-oxide, hydrate or any combination thereof.

[00092] In another embodiment, the present invention provides process for preparing a selective androgen receptor modulator (SARM) compound represented by the structure of formula III:



III

wherein X is O, NH, S, Se, PR or NR;

G is O or S;

T is OH, OR, -$NHCOCH_3$, or NHCOR

Z is NO_2, CN, COOH, COR, NHCOR or CONHR;

Y is CF_3, F, I, Br, Cl, CN, CR_3 or SnR_3;

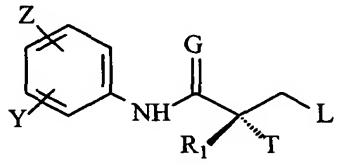
Q is N_3 or $NHCOCH_2Hal$;

Hal is halogen; and

R is alkyl, haloalkyl, dihaloalkyl, trihaloalkyl, CH_2F, CHF_2, CF_3, CF_2CF_3, aryl, phenyl, halogen, alkenyl or OH; and

R_1 is CH_3, CH_2F, CHF_2, CF_3, CH_2CH_3, or CF_2CF_3;

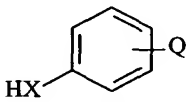
the process comprising the step of coupling a compound of formula XIV:



XIV

wherein Z, Y, G R_1 and T are as defined above and L is a leaving group,

with a compound of formula XV:



XV

wherein Q and X are as defined above.

[00093] In one embodiment, the coupling step is carried out in the presence of a base. In another embodiment, the leaving group L is Br. In another embodiment, the compound of formula XIV is prepared by

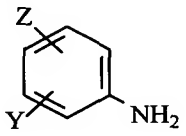
a. preparing a compound

formula X by ring opening of a cyclic compound of formula XI

XI X

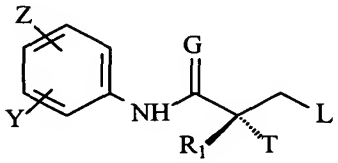
wherein L, R_1, and T are as defined above, G is O and T_1 is O or NH; and

b. reacting an amine of formula XVI



XVI

with the compound of formula X in the presence of a coupling reagent, to produce the compound of formula XIV.

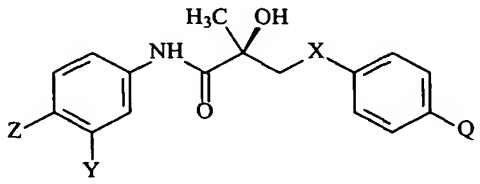


XIV

[00094] In one embodiment, step (a) is carried out in the presence of HBr. In another embodiment, the process further comprises the step of converting the selective androgen receptor modulator (SARM) compound to its analog, isomer, metabolite, derivative,

pharmaceutically acceptable salt, pharmaceutical product, N-oxide, hydrate or any combination thereof.

[00095] In another embodiment, the present invention provides process for preparing a selective androgen receptor modulator (SARM) compound represented by the structure of formula IV:



IV

wherein X is O, NH, S, Se, PR, or NR;

Z is NO_2, CN, COOH, COR, NHCOR or CONHR;

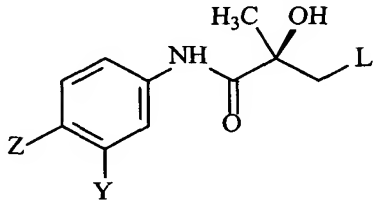
Y is CF_3, F, I, Br, Cl, CN, CR_3 or SnR_3;

Q is N_3 or $NHCOCH_2Hal$;

Hal is halogen; and

R is alkyl, haloalkyl, dihaloalkyl, trihaloalkyl, CH_2F, CHF_2, CF_3, CF_2CF_3, aryl, phenyl, halogen, alkenyl or OH;

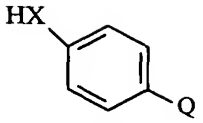
the process comprising the step of coupling an amide of formula XVII:



XVII

wherein Z and Y are as defined above and L is a leaving group,

with a compound of formula XVIII:

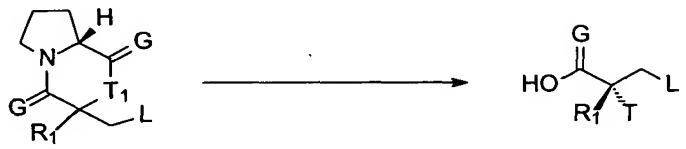


XVIII

wherein Q and X R_2 are as defined above.

[00096] In one embodiment, the coupling step is carried out in the presence of a base. In another embodiment, the leaving group L is Br. In another embodiment, the compound of formula XVII is prepared by

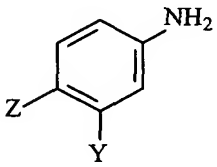
a. preparing a compound formula X by ring opening of a cyclic compound of formula XI



XI X

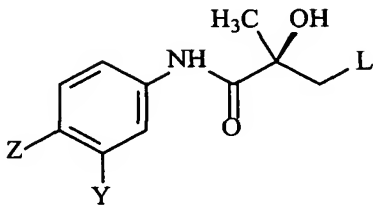
wherein L, R_1, and T are as defined above, G is O and T_1 is O or NH; and

b. reacting an amine of formula XVIX



XVIX

with the compound of formula X in the presence of a coupling reagent, to produce the compound of formula XVII.



XVII

In one embodiment, step (a) is carried out in the presence of HBr. In another embodiment, the process further comprises the step of purifying the SARM compound using a mixture of ethanol and water. In another embodiment, the process further comprises the step of converting the selective androgen receptor modulator (SARM) compound to its analog, isomer, metabolite, derivative, pharmaceutically acceptable salt, pharmaceutical product, N-oxide, hydrate or any combination thereof.

[00097] As demonstrated herein, Applicants have found that when the purification step of the SARM compounds is carried out in the presence of a nontoxic organic solvent and water, such as ethanol and water, for example by recrystallization from a mixture of ethanol and water, a highly pure product with excellent crystal stability is obtained in high yields. In addition, the use of a nontoxic organic solvent/water for purification is safe and cheap, and avoids any biological hazards that may arise from the use of toxic organic solvents such as hexane. In one embodiment, the nontoxic organic solvent is ethanol.

[00098] Thus, in one embodiment, the present invention provides a synthetic process for preparing the SARM compounds described herein, which involves a purification step comprising crystallization of the SARM product using a mixture of a nontoxic organic solvent and water. In one embodiment, the nontoxic organic solvent is ethanol. In a particular embodiment, the crystallization step comprises mixing an ethanol solution comprising the SARM compound with water, so as to crystallize the SARM compound.

In a further embodiment, the process further comprises the step of collecting the SARM compound by filtration.

[00099] The process of the present invention is suitable for large-scale preparation, since all of the steps give rise to highly pure compounds, thus avoiding complicated purification procedures which ultimately lower the yield. Thus the present invention provides methods for the synthesis of non-steroidal agonist compounds, that can be used for industrial large-scale synthesis, and that provide highly pure products in high yield. In addition, the methods described by the present invention utilize safe, environmentally friendly and cheap reagents and purification steps, thus avoiding any undesirable toxicological issues that may arise from the use of toxic, environmentally unfriendly or biologically unstable reagents.

[000100] It should be apparent to a person skilled in the art that any nontoxic organic solvent is suitable in the methods of the present invention, for example alcohols such as methanol or ethanol, aromatic compounds such as toluene and xylene, DMSO, THF, cyclohexane and the like.

[000101] In one embodiment, the nontoxic organic solvent is ethanol. Any grade and purity level of ethanol is suitable. In one embodiment, the ethanol is neat ethanol. In another embodiment, the ethanol is an ethanol solution that contains denaturants, such as toluene, methanol and the like.

[000102] It is understood to ta person skilled in the art that when T_1 is O or NH, T is compound VIII is O or NH_2. Thus, when T in compound I is OR, the reaction will involve a further step of converting the OH to OR by a reaction with, for example, an alkyl halide R-X. When T in compound I is NHCOR, $NHCOCH_3$, the reaction will involve a further step of converting the NH_2 to NHCOR or$NHCOCH_3$, by a reaction with, for example, the corresponding acyl chloride ClCOR or $ClCOCH_3$.

[000103] In one embodiment, the coupling step defined hereinabove is carried out in the presence of a base. Any suitable base that will deprotonate the hydrogen of the –XH

moiety (for example, a phenol moiety when X is O) and allow the coupling may be used. Nonlimiting examples of bases are carbonates such as alkali carbonates, for example sodium carbonate (Na_2CO_3), potassium carbonate (K_2CO_3) and cesium carbonate (Cs_2CO_3); bicarbonates such as alkali metal bicarbonates, for example sodium bicarbonate ($NaHCO_3$), potassium bicarbonate ($KHCO_3$), alkali metal hydrides such as sodium hydride (NaH), potassium hydride (KH) and lithium hydride (LiH), and the like.

[000104] The leaving group L is defined herein as any removable group customarily considered for chemical reactions, as will be known to the person skilled in the art. Suitable leaving groups are halogens, for example F, Cl, Br and I; alkyl sulfonate esters ($-OSO_2R$) wherein R is an alkyl group, for example methanesulfonate (mesylate), trifluoromethanesulfonate, ethanesulfonate, 2,2,2-trifluoroethanesulfonate, perfluoro butanesulfonate; aryl sulfonate esters ($-OSO_2Ar$) wherein Ar is an aryl group, for example p-toluoylsulfonate (tosylate), benzenesulphonate which may be unsubstituted or substituted by methyl, chlorine, bromine, nitro and the like; NO_3, NO_2, or sulfate, sulfite, phosphate, phosphite, carboxylate, imino ester, N_2 or carbamate.

[000105] The reaction is conveniently carried out in a suitable inert solvent or diluent such as, for example, tetrahydrofuran, diethyl ether, aromatic amines such as pyridine; aliphatic and aromatic hydrocarbons such as benzene, toluene, and xylene; dimethylsulfoxide (DMSO), dimethylformamide (DMF), and dimethylacetamide (DMAC). The reaction is suitably carried out at a temperature in the range, for example, -20 to 120 C., for example at or near ambient temperature.

[000106] The coupling reagent defined hereinabove is a reagent capable of turning the carboxylic acid/ thiocarboxylic acid of formula X into a reactive derivative thereof, thus enabling coupling with the respective amine amine to form an amide/thioamide bond. A suitable reactive derivative of a carboxylic acid / thiocarboxylic acid is, for example, an acyl halide / thioacyl halide, for example an acyl / thioacyl chloride formed by the reaction of the acid / thioacid and an inorganic acid chloride, for example thionyl chloride; a mixed anhydride, for example an anhydride formed by the reaction of the acid and a chloroformate such as isobutyl chloroformate; an active ester/thioester, for

example an ester/thioester formed by the reaction of the acid/thioacid and a phenol, an ester/thioester or an alcohol such as methanol, ethanol, isopropanol, butanol or N-hydroxybenzotriazole; an acyl/thioacyl azide, for example an azide formed by the reaction of the acid/thioacid and azide such as diphenylphosphoryl azide; an acyl cyanide/thioacyl cyanide, for example a cyanide formed by the reaction of an acid and a cyanide such as diethylphosphoryl cyanide; or the product of the reaction of the acid/thioacid and a carbodiimide such as dicyclohexylcarbodiimide.

[000107] The reaction is conveniently carried out in a suitable inert solvent or diluent as described hereinabove, suitably in the presence of a base such as triethylamine, and at a temperature in the range, as desribed above.

Biological Activity of Selective Androgen Modulator Compounds

[000108] The SARM compounds provided herein are selective androgen receptor modulators (SARM). Several of these agents have an antiandrogenic activity of a nonsteroidal ligand for the androgen receptor. Another group of these agents have an androgenic activity of a nonsteroidal ligand for the androgen receptor. Furthermore, several of the SARM compounds bind irreversibly to the androgen receptor.

[000109] In another embodiment of the present invention, the compounds described herein are active via a biological mechanism that is independent of the androgen receptor, as described in detail hereinbelow.

[000110] It should however be apparent to a person skilled in the art that the mechanism by which the compounds of the present invention exert their biological effect should not be construed as a limitation to the broad scope of the present invention, which encompasses a wide spectrum of compounds and their therapeutic use for a) male contraception; b) treatment of a variety of hormone-related conditions, for example conditions associated with Androgen Decline in Aging Male (ADAM), such as fatigue, depression, decreased libido, sexual dysfunction, erectile dysfunction, hypogonadism, osteoporosis, hair loss, anemia, obesity, sarcopenia, osteopenia,osteoporosis, benign prostate hyperplasia, alterations in mood and cognition and prostate cancer; c) treatment

of conditions associated with ADIF, such as sexual dysfunction, decreased sexual libido, hypogonadism, sarcopenia, osteopenia, osteoporosis, alterations in cognition and mood, depression, anemia, hair loss, obesity, endometriosis, breast cancer, uterine cancer and ovarian cancer; d) treatment and/or prevention of acute and/or chronic muscular wasting conditions; e) preventing and/or treating dry eye conditions; f) oral androgen replacement therapy; g) decreasing the incidence of, halting or causing a regression of cancer cells; and/or h) inducing apoptosis in a cancer cell; and/or i) inducing cell cycle arrest; and/or j) inhibiting and/or suppressing cellular proliferation.

[000111] As used herein, receptors for extracellular signaling molecules are collectively referred to as "cell signaling receptors". Many cell signaling receptors are transmembrane proteins on a cell surface; when they bind an extracellular signaling molecule (i.e., a ligand), they become activated so as to generate a cascade of intracellular signals that alter the behavior of the cell. In contrast, in some cases, the receptors are inside the cell and the signaling ligand has to enter the cell to activate them; these signaling molecules therefore must be sufficiently small and hydrophobic to diffuse across the plasma membrane of the cell.

[000112] Steroid hormones are one example of small hydrophobic molecules that diffuse directly across the plasma membrane of target cells and bind to intracellular cell signaling receptors. These receptors are structurally related and constitute the intracellular receptor superfamily (or steroid-hormone receptor superfamily). Steroid hormone receptors include progesterone receptors, estrogen receptors, androgen receptors, glueocorticoid receptors, and mineralocorticoid receptors. In one embodiment, the present invention is directed to androgen receptors.

[000113] In addition to ligand binding to the receptors, the receptors can be blocked to prevent ligand binding. When a substance binds to a receptor, the three-dimensional structure of the substance fits into a space created by the three- dimensional structure of the receptor in a ball and socket configuration. The better the ball fits into the socket, the more tightly it is held. This phenomenon is called affinity. If the affinity of a substance is greater than the original hormone, it will compete with the hormone and bind the

binding site more frequently. Once bound, signals may be sent through the receptor into the cells, causing the cell to respond in some fashion. This is called activation. On activation, the activated receptor then directly regulates the transcription of specific genes. But the substance and the receptor may have certain attributes, other than affinity, in order to activate the cell. Chemical bonds between atoms of the substance and the atoms of the receptors may form. In some cases, this leads to a change in the configuration of the receptor, which is enough to begin the activation process (called signal transduction).

[000114] In another embodiment, the present invention is directed to selective androgen receptor modulator compounds, which are antagonist compounds. A receptor agonist is a substance, which binds receptors and activates them. A receptor antagonist is a substance which binds receptors and inactivates them. Thus, in one embodiment, the SARM compounds of the present invention are useful in binding to and inactivating steroidal hormone receptors. In one embodiment, the antagonist compound of the present invention is an antagonist which binds the androgen receptor. In another embodiment, the compound has high affinity for the androgen receptor.

[000115] Assays to determine whether the compounds of the present invention are AR agonists or antagonists are well known to a person skilled in the art. For example, AR agonistic activity can be determined by monitoring the ability of the SARM compounds to maintain and/or stimulate the growth of AR containing tissue such as prostate and seminal vesicles, as measured by weight. AR antagonistic activity can be determined by monitoring the ability of the SARM compounds inhibit the growth of AR containing tissue.

[000116] An androgen receptor is an androgen receptor of any species, for example a mammal. In one embodiment, the androgen receptor is an androgen receptor of a human.

[000117] The compounds of the present invention bind either reversibly or irreversibly to an androgen receptor. In one embodiment, the SARM compounds bind reversibly to an

androgen receptor. In another embodiment, the SARM compounds bind reversibly to an androgen receptor of a mammal. In another embodiment, the SARM compounds bind reversibly to an androgen receptor of a human. Reversible binding of a compound to a receptor means that a compound can detach from the receptor after binding.

[000118] In another embodiment, the SARM compounds bind irreversibly to an androgen receptor. In one embodiment, the SARM compounds bind irreversibly to an androgen receptor of a mammal. In another embodiment, the SARM compounds bind irreversibly to an androgen receptor of a human. Thus, in one embodiment, the compounds of the present invention may contain a functional group (e.g. affinity label) that allows alkylation of the androgen receptor (i.e. covalent bond formation). Thus, in this case, the compounds are alkylating agents which bind irreversibly to the receptor and, accordingly, cannot be displaced by a steroid, such as the endogenous ligands DHT and testosterone. An "alkylating agent" is defined herein as an agent which alkylates (forms a covalent bond) a cellular component, such as DNA, RNA or enzyme. It is a highly reactive chemical that introduces alkyl radicals into biologically active molecules and thereby prevents their proper functioning. The alkylating moiety is an electrophilic group that interacts with nucleophilic moieties in cellular components. For example, in one embodiment, an alkylating group is an isocyanate moiety, an electrophilic group which forms covalent bonds with nucleophilic groups (N, O, S etc.) in cellular components. In another embodiment, an alkylating group is an isothiocyanate moiety, another electrophilic group which forms covalent bonds with nucleophilic groups (N, O, S etc.) in cellular components. In another embodiment, an alkylating group is a haloalkyl (CH_2Hal wherein Hal is halogen), an electrophilic group which forms covalent bonds with nucleophilic groups in cellular components. In another embodiment, an alkylating group is a haloalkyl-amido ($NHCOCH_2X$ wherein X is halogen), an electrophilic group which forms covalent bonds with nucleophilic groups in cellular components.

[000119] In another embodiment of the present invention, the compounds described herein are active via a biological mechanism that is independent of the androgen receptor. Thus, in one embodiment, the compounds of the present invention bind to a cellular component, either reversibly or reversibly. In another embodiment, the compounds

further alkylate the cellular component. A "cellular component" is defined herein as any intracellular, extracellular, membrane bound component found in a cell.

[000120] The compounds of the present invention bind either reversibly or irreversibly to the cellular component. In one embodiment, the compounds bind reversibly to the cellular component. In another embodiment, the compounds bind irreversibly to the cellular component of a mammal. In another embodiment, the compounds bind reversibly to the cellular component of a human. Reversible binding of a compound to a receptor means that a compound can detach from the receptor after binding.

[000121] In another embodiment, the compounds further alkylate the cellular component. Thus, in one embodiment, the compounds of the present invention may contain a functional group (e.g. affinity label) that allows alkylation of the cellular component (i.e. covalent bond formation). Thus, in this case, the compounds are alkylating agents which bind irreversibly to the receptor and, accordingly, cannot be displaced. An "alkylating agent" is as defined above.

[000122] Thus, in one embodiment, the present invention further provides a method of binding a selective androgen receptor modulator compound to a cellular component, including an androgen receptor, comprising the step of contacting the cellular component with the selective androgen receptor modulator compound of the present invention, and/or its analog, derivative, isomer, metabolite, pharmaceutically acceptable salt, pharmaceutical product, hydrate, N-oxide or any combination thereof, in an amount effective to bind the selective androgen receptor modulator compound to the cellular component. In one embodiment, the cellular component is an androgen receptor.

[000123] In another embodiment, the present invention further provides a method of irreversibly binding a selective androgen receptor modulator compound to a cellular component, comprising the step of contacting the cellular component with the selective androgen receptor modulator compound of the present invention, and/or its analog, derivative, isomer, metabolite, pharmaceutically acceptable salt, pharmaceutical product, hydrate, N-oxide or any combination thereof, in an amount effective to irreversibly bind

the selective androgen receptor modulator compound to the cellular component. In one embodiment, the cellular component is an androgen receptor.

[000124] In another embodiment, the present invention further provides a method of alkylating a cellular component, comprising the step of contacting the cellular component with the selective androgen receptor modulator compound of the present invention, and/or its analog, derivative, isomer, metabolite, pharmaceutically acceptable salt, pharmaceutical product, hydrate, N-oxide or any combination thereof, in an amount effective to alkylate the cellular component. In one embodiment, the cellular component is an androgen receptor.

[000125] In another embodiment, the present invention provides a method of suppressing spermatogenesis in a subject, comprising the step of administering to the subject the selective androgen receptor modulator compound of any of formulas I-IV and/or its analog, derivative, isomer, metabolite, pharmaceutically acceptable salt, pharmaceutical product, hydrate, N-oxide or any combination thereof, in an amount effective to suppress sperm production.

[000126] In another embodiment, the present invention provides a method of contraception in a male subject, comprising the step of administering to the subject the selective androgen receptor modulator compound of any of formulas I-IV and/or its analog, derivative, isomer, metabolite, pharmaceutically acceptable salt, pharmaceutical product, hydrate, N-oxide or any combination thereof, in an amount effective to suppress sperm production in the subject, thereby effecting contraception in the subject.

[000127] In another embodiment, the present invention further provides a method of hormone therapy, comprising the step of administering to the subject the selective androgen receptor modulator compound of any of any of formulas I-IV and/or its analog, derivative, isomer, metabolite, pharmaceutically acceptable salt, pharmaceutical product, hydrate, N-oxide or any combination thereof, in an amount effective to bind the selective androgen receptor modulator compound to the androgen receptor and effect a change in an androgen-dependent condition.

[000128] In another embodiment, the present invention provides a method of hormone replacement therapy comprising the step of administering to the subject the selective androgen receptor modulator compound of any of formulas I-IV and/or its analog, derivative, isomer, metabolite, pharmaceutically acceptable salt, pharmaceutical product, hydrate, N-oxide or any combination thereof, in an amount effective to effect a change in an androgen-dependent condition.

[000129] In another embodiment, the present invention further provides a method of treating a subject having a hormone related condition, comprising the step of administering to the subject the selective androgen receptor modulator compound of any of any of formulas I-IV and/or its analog, derivative, isomer, metabolite, pharmaceutically acceptable salt, pharmaceutical product, hydrate, N-oxide or any combination thereof, in an amount effective to bind the selective androgen receptor modulator compound to the androgen receptor and effect a change in an androgen-dependent condition.

[000130] In another embodiment, the present invention further provides a method of treating a subject suffering from prostate cancer, comprising the step of administering to the subject the selective androgen receptor modulator compound of any of formulas I-IV and/or its analog, derivative, isomer, metabolite, pharmaceutically acceptable salt, pharmaceutical product, hydrate, N-oxide or any combination thereof, in an amount effective to treat prostate cancer in the subject.

[000131] In another embodiment, the present invention provides a method of preventing prostate cancer in a subject, comprising the step of administering to the subject the selective androgen receptor modulator compound of formulas I-IV and/or its analog, derivative, isomer, metabolite, pharmaceutically acceptable salt, pharmaceutical product, hydrate, N-oxide or any combination thereof, in an amount effective to prevent prostate cancer in the subject.

[000132] In another embodiment, the present invention further provides a method of delaying the progression of prostate cancer in a subject suffering from prostate cancer, comprising the step of administering to the subject the selective androgen receptor modulator compound of any of any of formulas I-IV and/or its analog, derivative, isomer, metabolite, pharmaceutically acceptable salt, pharmaceutical product, hydrate, N-oxide or any combination thereof, in an amount effective to delay the progression of prostate cancer in the subject.

[000133] In another embodiment, the present invention further provides a method of preventing the recurrence of prostate cancer in a subject suffering from prostate cancer, comprising the step of administering to the subject the selective androgen receptor modulator compound of any of any of formulas I-IV and/or its analog, derivative, isomer, metabolite, pharmaceutically acceptable salt, pharmaceutical product, hydrate, N-oxide or any combination thereof, in an amount effective to prevent the recurrence of prostate cancer in the subject.

[000134] In another embodiment, the present invention provides a method of treating the recurrence of prostate cancer in a subject suffering from prostate cancer, comprising the step of administering to the subject the selective androgen receptor modulator compound of any of any of formulas I-IV and/or its analog, derivative, isomer, metabolite, pharmaceutically acceptable salt, pharmaceutical product, hydrate, N-oxide or any combination thereof, in an amount effective to treat the recurrence of prostate cancer in the subject.

[000135] In another embodiment, the present invention provides a method of treating a dry eye condition in a subject suffering from dry eyes, comprising the step of administering to said subject the selective androgen receptor modulator compound of formulas I-IV and/or its analog, derivative, isomer, metabolite, pharmaceutically acceptable salt, pharmaceutical product, hydrate or N-oxide or any combination thereof, in an amount effective to treat dry eyes in the subject.

[000136] In another embodiment, the present invention provides a method of preventing a dry eye condition in a subject, comprising the step of administering to said subject the selective androgen receptor modulator compound of formulas I-IV and/or its analog, derivative, isomer, metabolite, pharmaceutically acceptable salt, pharmaceutical product, hydrate or N-oxide or any combination thereof, in an amount effective to prevent dry eyes in the subject.

[000137] In another embodiment, the present invention provides a method of inducing apoptosis in a prostate cancer cell, comprising the step of contacting the cell with the selective androgen receptor modulator compound of any of any of formulas I-IV and/or its analog, derivative, isomer, metabolite, pharmaceutically acceptable salt, pharmaceutical product, hydrate, N-oxide or any combination thereof, in an amount effective to induce apoptosis in the cancer cell.

[000138] As defined herein, "apoptosis", or programmed cell death, is a form of cell death in which a programmed sequence of events leads to the elimination of cells without releasing harmful substances into the surrounding area. Apoptosis plays a crucial role in developing and maintaining health by eliminating old cells, unnecessary cells, and unhealthy cells.

[000139] As defined herein, "contacting" means that the SARM compound of the present invention is introduced into a sample containing the enzyme in a test tube, flask, tissue culture, chip, array, plate, microplate, capillary, or the like, and incubated at a temperature and time sufficient to permit binding of the SARM to the enzyme. Methods for contacting the samples with the SARM or other specific binding components are known to those skilled in the art and may be selected depending on the type of assay protocol to be run. Incubation methods are also standard and are known to those skilled in the art.

[000140] In another embodiment, the term "contacting" means that the SARM compound of the present invention is introduced into a subject receiving treatment, and the SARM compound is allowed to come in contact with the androgen receptor *in vivo*.

[000141] As used herein, the term "treating" includes preventative as well as disorder remitative treatment. As used herein, the terms "reducing", "suppressing" and "inhibiting" have their commonly understood meaning of lessening or decreasing. As used herein, the term "progression" means increasing in scope or severity, advancing, growing or becoming worse. As used herein, the term "recurrence" means the return of a disease after a remission. As used herein, the term "delaying" means stopping, hindering, slowing down, postponing, holding up or setting back.

[000142] As used herin, the term "administering" refers to bringing a subject in contact with a SARM compound of the present invention. As used herein, administration can be accomplished *in vitro*, i.e. in a test tube, or *in vivo*, i.e. in cells or tissues of living organisms, for example humans. In one embodiment, the present invention encompasses administering the compounds of the present invention to a subject.

[000143] The term "libido, as used herein, means sexual desire.

[000144] The term "erectile", as used herein, means capable of being erected. An erectile tissue is a tissue, which is capable of being greatly dilated and made rigid by the distension of the numerous blood vessels which it contains.

[000145] "Hypogonadism" is a condition resulting from or characterised by abnormally decreased functional activity of the gonads, with retardation of growth and sexual development. "Osteopenia" refers to decreased calcification or density of bone. This is a term which encompasses all skeletal systems in which such a condition is noted.

[000146] "Osteoporosis" refers to a thinning of the bones with reduction in bone mass due to depletion of calcium and bone protein. Osteoporosis predisposes a person to fractures, which are often slow to heal and heal poorly. Unchecked osteoporosis can lead to changes in posture, physical abnormality, and decreased mobility.

[000147] "BPH (benign prostate hyperplasia)" is a nonmalignant enlargement of the prostate gland, and is the most common non-malignant proliferative abnormality found in any internal organ and the major cause of morbidity in the adult male. BPH occurs in over 75% of men over 50 years of age, reaching 88% prevalence by the ninth decade. BPH frequently results in a gradual squeezing of the portion of the urethra which traverses the prostate (prostatic urethra). This causes patients to experience a frequent urge to urinate because of incomplete emptying of the bladder and urgency of urination. The obstruction of urinary flow can also lead to a general lack of control over urination, including difficulty initiating urination when desired, as well as difficulty in preventing urinary flow because of the inability to empty urine from the bladder, a condition known as overflow urinary incontinence, which can lead to urinary obstruction and to urinary failure.

[000148] "Cognition" refers to the process of knowing, specifically the process of being aware, knowing, thinking, learning and judging. Cognition is related to the fields of psychology, linguistics, computer science, neuroscience, mathematics, ethology and philosophy. The term "mood" refers to a temper or state of the mind. As contemplated herein, alterations means any change for the positive or negative, in cognition and/or mood.

[000149] The term "depression" refers to an illness that involves the body, mood and thoughts, that affects the way a person eats, sleeps and the way one feels about oneself, and thinks about things. The signs and symptoms of depression include loss of interest in activities, loss of appetite or overeating, loss of emotional expression, an empty mood, feelings of hopelessness, pessimism, guilt or helplessness, social withdrawal, fatigue, sleep disturbances, trouble concentrating, remembering, or making decisions, restlessness, irritability, headaches, digestive disorders or chronic pain.

[000150] The term "hair loss", medically known as alopecia, refers to baldness as in the very common type of male-pattern baldness. Baldness typically begins with patch hair loss on the scalp and sometimes progresses to complete baldness and even loss of body hair. Hair loss affects both males and females.

[000151] "Anemia" refers to the condition of having less than the normal number of red blood cells or less than the normal quantity of hemoglobin in the blood. The oxygen-carrying capacity of the blood is, therefore, decreased. Persons with anemia may feel tired and fatigue easily, appear pale, develop palpitations and become usually short of breath. Anemia is caused by four basic factors: a) hemorrhage (bleeding); b) hemolysis (excessive destruction of red blood cells); c) underproduction of red blood cells; and d) not enough normal hemoglobin. There are many forms of anemia, including aplastic anemia, benzene poisoning, Fanconi anemia, hemolytic disease of the newborn, hereditary spherocytosis, iron deficiency anemia, osteopetrosis, pernicious anemia, sickle cell disease, thalassemia, myelodysplastic syndrome, and a variety of bone marrow diseases. As contemplated herein, the SARM compounds of the present invention are useful in preventing and/or treating any one or more of the above-listed forms of anemia.

[000152] "Obesity" refers to the state of being well above one's normal weight. Traditionally, a person is considered to be obese if they are more than 20 percent over their ideal weight. Obesity has been more precisely defined by the National Institute of Health (NIH) as a Body to Mass Index (BMI) of 30 or above. Obesity is often multifactorial, based on both genetic and behavioral factors. Overweight due to obesity is a significant contributor to health problems. It increases the risk of developing a number of diseases including: Type 2 (adult-onset) diabetes; high blood pressure (hypertension); stroke (cerebrovascular accident or CVA); heart attack (myocardial infarction or MI); heart failure (congestive heart failure); cancer (certain forms such as cancer of the prostate and cancer of the colon and rectum); gallstones and gallbladder disease (cholecystitis); Gout and gouty arthritis; osteoarthritis (degenerative arthritis) of the knees, hips, and the lower back; sleep apnea (failure to breath normally during sleep, lowering blood oxygen); and Pickwickian syndrome (obesity, red face, underventilation and drowsiness). As contemplated herein, the term "obesity" includes any one of the above-listed obesity-related conditions and diseases. Thus the SARM compounds of the present invention are useful in preventing and/or treating obesity and any one or more of the above-listed obesity-related conditions and diseases.

[000153] "Prostate cancer" is one of the most frequently occurring cancers among men in the United States, with hundreds of thousands of new cases diagnosed each year. Over sixty percent of newly diagnosed cases of prostate cancer are found to be pathologically advanced, with no cure and a dismal prognosis. One third of all men over 50 years of age have a latent form of prostate cancer that may be activated into the life-threatening clinical prostate cancer form. The frequency of latent prostatic tumors has been shown to increase substantially with each decade of life from the 50s (5.3-14%) to the 90s (40-80%). The number of people with latent prostate cancer is the same across all cultures, ethnic groups, and races, yet the frequency of clinically aggressive cancer is markedly different. This suggests that environmental factors may play a role in activating latent prostate cancer.

[000154] In one embodiment, the methods of the present invention comprise comprise administering a SARM compound as the sole active ingredient. However, also encompassed within the scope of the present invention are methods for hormone therapy, for treating prostate cancer, for delaying the progression of prostate cancer, and for preventing and/or treating the recurrence of prostate cancer, which comprise administering the SARM compounds in combination with one or more therapeutic agents. These agents include, but are not limited to: LHRH analogs, reversible antiandrogens, antiestrogens, anticancer drugs, 5-alpha reductase inhibitors, aromatase inhibitors, progestins, agents acting through other nuclear hormone receptors, selective estrogen receptor modulators (SERM), progesterone, estrogen, PDE5 inhibitors, apomorphine, bisphosphonate, and one or more additional SARMS.

[000155] Thus, in one embodiment, the methods of the present invention comprise administering the selective androgen receptor modulator compound, in combination with an LHRH analog. In another embodiment, the methods of the present invention comprise administering a selective androgen receptor modulator compound, in combination with a reversible antiandrogen. In another embodiment, the methods of the present invention comprise administering a selective androgen receptor modulator compound, in combination with an antiestrogen. In another embodiment, the methods of

the present invention comprise administering a selective androgen receptor modulator compound, in combination with an anticancer drug. In another embodiment, the methods of the present invention comprise administering a selective androgen receptor modulator compound, in combination with a 5-alpha reductase inhibitor. In another embodiment, the methods of the present invention comprise administering a selective androgen receptor modulator compound, in combination with an aromatase inhibitor. In another embodiment, the methods of the present invention comprise administering a selective androgen receptor modulator compound, in combination with a progestin. In another embodiment, the methods of the present invention comprise administering a selective androgen receptor modulator compound, in combination with an agent acting through other nuclear hormone receptors. In another embodiment, the methods of the present invention comprise administering a selective androgen receptor modulator compound, in combination with a selective estrogen receptor modulators (SERM). In another embodiment, the methods of the present invention comprise administering a selective androgen receptor modulator compound, in combination with a progesterone. In another embodiment, the methods of the present invention comprise administering a selective androgen receptor modulator compound, in combination with an estrogen. In another embodiment, the methods of the present invention comprise administering a selective androgen receptor modulator compound, in combination with a PDE5 inhibitor. In another embodiment, the methods of the present invention comprise administering a selective androgen receptor modulator compound, in combination with apomorphine. In another embodiment, the methods of the present invention comprise administering a selective androgen receptor modulator compound, in combination with a bisphosphonate. In another embodiment, the methods of the present invention comprise administering a selective androgen receptor modulator compound, in combination with one or more additional SARMS.

Pharmaceutical Compositions

[000156] In one embodiment, the present invention provides a composition comprising the selective androgen receptor modulator compound of the present invention and/or its

analog, derivative, isomer, metabolite, pharmaceutically acceptable salt, pharmaceutical product, hydrate, N-oxide or any combination thereof.

[000157] In another embodiment, the present invention provides a pharmaceutical composition comprising the selective androgen receptor modulator compound of the present invention and/or its analog, derivative, isomer, metabolite, pharmaceutical product, hydrate, N-oxide or any combination thereof; and a suitable carrier or diluent.

[000158] As used herein, "pharmaceutical composition" means therapeutically effective amounts of the SARM together with suitable diluents, preservatives, solubilizers, emulsifiers, adjuvant and/or carriers. A "therapeutically effective amount" as used herein refers to that amount which provides a therapeutic effect for a given condition and administration regimen. Such compositions are liquids or Lyophilized or otherwise dried formulations and include diluents of various buffer content (e.g., Tris-HCI., acetate, phosphate), pH and ionic strength, additives such as albumin or gelatin to prevent absorption to surfaces, detergents (e.g., Tween 20, Tween 80, Pluronic F68, bile acid salts), solubilizing agents (e.g., glycerol, polyethylene glycerol), anti-oxidants (e.g., ascorbic acid, sodium metabisulfite), preservatives (e.g., Thimerosal, benzyl alcohol, parabens), bulking substances or tonicity modifiers (e.g., lactose, mannitol), covalent attachment of polymers such as polyethylene glycol to the protein, complexation with metal ions, or incorporation of the material into or onto particulate preparations of polymeric compounds such as polylactic acid, polglycolic acid, hydrogels, etc, or onto liposomes, microemulsions, micelles, unilamellar or multilamellar vesicles, erythrocyte ghosts, or spheroplasts.) Such compositions will influence the physical state, solubility, stability, rate of *in vivo* release, and rate of *in vivo* clearance. Controlled or sustained release compositions include formulation in lipophilic depots (e.g., fatty acids, waxes, oils).

[000159] Also comprehended by the invention are particulate compositions coated with polymers (e.g., poloxamers or poloxamines). Other embodiments of the compositions of the invention incorporate particulate forms protective coatings, protease inhibitors or permeation enhancers for various routes of administration, including parenteral,

pulmonary, nasal and oral. In one embodiment the pharmaceutical composition is administered parenterally, paracancerally, transmucosally, transdermally, intramuscularly, intravenously, intradermally, subcutaneously, intraperitonealy, intraventricularly, intravaginally, intracranially and intratumorally.

[000160] Further, as used herein "pharmaceutically acceptable carriers" are well known to those skilled in the art and include, but are not limited to, 0.01-0.1M and preferably 0.05M phosphate buffer or 0.8% saline. Additionally, such pharmaceutically acceptable carriers may be aqueous or non-aqueous solutions, suspensions, and emulsions. Examples of non-aqueous solvents are propylene glycol, polyethylene glycol, vegetable oils such as olive oil, and injectable organic esters such as ethyl oleate. Aqueous carriers include water, alcoholic/aqueous solutions, emulsions or suspensions, including saline and buffered media.

[000161] Parenteral vehicles include sodium chloride solution, Ringer's dextrose, dextrose and sodium chloride, lactated Ringer's and fixed oils. Intravenous vehicles include fluid and nutrient replenishers, electrolyte replenishers such as those based on Ringer's dextrose, and the like. Preservatives and other additives may also be present, such as, for example, antimicrobials, antioxidants, collating agents, inert gases and the like.

[000162] Controlled or sustained release compositions include formulation in lipophilic depots (e.g. fatty acids, waxes, oils). Also comprehended by the invention are particulate compositions coated with polymers (e.g. poloxamers or poloxamines) and the compound coupled to antibodies directed against tissue-specific receptors, ligands or antigens or coupled to ligands of tissue-specific receptors.

[000163] Other embodiments of the compositions of the invention incorporate particulate forms, protective coatings, protease inhibitors or permeation enhancers for various routes of administration, including parenteral, pulmonary, nasal and oral.

[000164] Compounds modified by the covalent attachment of water-soluble polymers such as polyethylene glycol, copolymers of polyethylene glycol and polypropylene

glycol, carboxymethyl cellulose, dextran, polyvinyl alcohol, polyvinylpyrrolidone or polyproline are known to exhibit substantially longer half-lives in blood following intravenous injection than do the corresponding unmodified compounds (Abuchowski et al., 1981; Newmark et al., 1982; and Katre et al., 1987). Such modifications may also increase the compound's solubility in aqueous solution, eliminate aggregation, enhance the physical and chemical stability of the compound, and greatly reduce the immunogenicity and reactivity of the compound. As a result, the desired *in vivo* biological activity may be achieved by the administration of such polymer-compound abducts less frequently or in lower doses than with the unmodified compound.

[000165] In yet another embodiment, the pharmaceutical composition can be delivered in a controlled release system. For example, the agent may be administered using intravenous infusion, an implantable osmotic pump, a transdermal patch, liposomes, or other modes of administration. In one embodiment, a pump may be used (see Langer, supra; Sefton, CRC Crit. Ref. Biomed. Eng. 14:201 (1987); Buchwald et al., Surgery 88:507 (1980); Saudek et al., N. Engl. J. Med. 321:574 (1989). In another embodiment, polymeric materials can be used. In yet another embodiment, a controlled release system can be placed in proximity to the therapeutic target, i.e., the brain, thus requiring only a fraction of the systemic dose (see, e.g., Goodson, in Medical Applications of Controlled Release, supra, vol. 2, pp. 115-138 (1984). Other controlled release systems are discussed in the review by Langer (Science 249:1527-1533 (1990).

[000166] The pharmaceutical preparation can comprise the SARM agent alone, or can further include a pharmaceutically acceptable carrier, and can be in solid or liquid form such as tablets, powders, capsules, pellets, solutions, suspensions, elixirs, emulsions, gels, creams, or suppositories, including rectal and urethral suppositories. Pharmaceutically acceptable carriers include gums, starches, sugars, cellulosic materials, and mixtures thereof. The pharmaceutical preparation containing the SARMagent can be administered to a subject by, for example, subcutaneous implantation of a pellet; in a further embodiment, the pellet provides for controlled release of SARM agent over a period of time. The preparation can also be administered by intravenous, intraarterial, or intramuscular injection of a liquid preparation, oral administration of a liquid or solid

preparation, or by topical application. Administration can also be accomplished by use of a rectal suppository or a urethral suppository.

[000167] The pharmaceutical preparations of the invention can be prepared by known dissolving, mixing, granulating, or tablet-forming processes. For oral administration, the SARM agents or their physiologically tolerated derivatives such as salts, esters, N-oxides, and the like are mixed with additives customary for this purpose, such as vehicles, stabilizers, or inert diluents, and converted by customary methods into suitable forms for administration, such as tablets, coated tablets, hard or soft gelatin capsules, aqueous, alcoholic or oily solutions. Examples of suitable inert vehicles are conventional tablet bases such as lactose, sucrose, or cornstarch in combination with binders such as acacia, cornstarch, gelatin, with disintegrating agents such as cornstarch, potato starch, alginic acid, or with a lubricant such as stearic acid or magnesium stearate.

[000168] Examples of suitable oily vehicles or solvents are vegetable or animal oils such as sunflower oil or fish-liver oil. Preparations can be effected both as dry and as wet granules. For parenteral administration (subcutaneous, intravenous, intraarterial, or intramuscular injection), the SARM agents or their physiologically tolerated derivatives such as salts, esters, N-oxides, and the like are converted into a solution, suspension, or emulsion, if desired with the substances customary and suitable for this purpose, for example, solubilizers or other auxiliaries. Examples are sterile liquids such as water and oils, with or without the addition of a surfactant and other pharmaceutically acceptable adjuvants. Illustrative oils are those of petroleum, animal, vegetable, or synthetic origin, for example, peanut oil, soybean oil, or mineral oil. In general, water, saline, aqueous dextrose and related sugar solutions, and glycols such as propylene glycols or polyethylene glycol are preferred liquid carriers, particularly for injectable solutions.

[000169] The preparation of pharmaceutical compositions which contain an active component is well understood in the art. Typically, such compositions are prepared as aerosols of the polypeptide delivered to the nasopharynx or as injectables, either as liquid solutions or suspensions; however, solid forms suitable for solution in, or suspension in, liquid prior to injection can also be prepared. The preparation can also be

emulsified. The active therapeutic ingredient is often mixed with excipients which are pharmaceutically acceptable and compatible with the active ingredient. Suitable excipients are, for example, water, saline, dextrose, glycerol, ethanol, or the like or any combination thereof.

[000170] In addition, the composition can contain minor amounts of auxiliary substances such as wetting or emulsifying agents, pH buffering agents which enhance the effectiveness of the active ingredient.

[000171] An active component can be formulated into the composition as neutralized pharmaceutically acceptable salt forms. Pharmaceutically acceptable salts include the acid addition salts (formed with the free amino groups of the polypeptide or antibody molecule), which are formed with inorganic acids such as, for example, hydrochloric or phosphoric acids, or such organic acids as acetic, oxalic, tartaric, mandelic, and the like. Salts formed from the free carboxyl groups can also be derived from inorganic bases such as, for example, sodium, potassium, ammonium, calcium, or ferric hydroxides, and such organic bases as isopropylamine, trimethylamine, 2-ethylamino ethanol, histidine, procaine, and the like.

[000172] For topical administration to body surfaces using, for example, creams, gels, drops, and the like, the SARM agents or their physiologically tolerated derivatives such as salts, esters, N-oxides, and the like are prepared and applied as solutions, suspensions, or emulsions in a physiologically acceptable diluent with or without a pharmaceutical carrier.

[000173] In another embodiment, the active compound can be delivered in a vesicle, in particular a liposome (see Langer, Science 249:1527-1533 (1990); Treat et al., in Liposomes in the Therapyof Infectious Disease and Cancer, Lopez- Berestein and Fidler (eds.), Liss, New York, pp. 353-365 (1989); Lopez-Berestein, ibid., pp. 317-327; see generally ibid).

[000174] For use in medicine, the salts of the SARM will be pharmaceutically acceptable salts. Other salts may, however, be useful in the preparation of the compounds according to the invention or of their pharmaceutically acceptable salts. Suitable pharmaceutically acceptable salts of the compounds of this invention include acid addition salts which may, for example, be formed by mixing a solution of the compound according to the invention with a solution of a pharmaceutically acceptable acid such as hydrochloric acid, sulphuric acid, methanesulphonic acid, fumaric acid, maleic acid, succinic acid, acetic acid, benzoic: acid, oxalic acid, citric acid, tartaric acid, carbonic acid or phosphoric acid.

[000175] The following examples are presented in order to more fully illustrate the preferred embodiments of the invention. They should in no way be construed, however, as limiting the broad scope of the invention.

EXPERIMENTAL DETAILS SECTION

EXAMPLE 1

EXPERIMENTAL METHODS

Cell Lines

[000176] The origins of the cell lines used in the studies described herein are shown in Table 1 below:

Table 1

Cell line	Morphology	Receptor espressed	Origin	Patient
LNCaP	Epithelial	Androgen; Estrogen	Needle aspiration biopsy of left supraclavicular lymph node	50-year-old white male with tage D1 prostatic cancer
DU 145	Epithelial		Metastatic CNS lesion	69-year-old white male with metastatic carcinoma of the prostate and a 3 year history of lymphocytic leukemia
PC-3	Epithelial		Prostatic metastatic bone marrow	62-year-old male Caucasian with grade IV prostatic adenocarcinoma
PPC-1 (primary prostate carcinoma-1)	Epithelial		Transurethral resection of the prostate	67-year-old black male with stage D2 poorly differentialted adenocarcinoma of prostate
TSU	Epithelial		Metastatic tumor in a cervical lymph node	73-year-old male Japanese with a moderately differentiated prostatic adenocarcinoma

Cell Culture

[000177] Prostate cancer cell lines were obtained from ATCC. All cells were grown in RPMI-1640 medium containing 2 mM L-glutamine supplemented with 10% fetal bovine serum (FBS) and maintained in a 5% CO2/95% air humidified atmosphere at 37°C.

Assay for Cell Growth Inhibition (Sulforhodamine B assay)

[000178] Cells were plated on 96-well plates and incubated with drug-containing culture medium (200 μL/well) for 4 (DU 145, PC-3, PPC-1, and TSU) or 6 (LNCaP)

days. Medium was replaced with freshly prepared batches every other day during the incubation. At the end of drug treatment, an aliquot of 50 μL of cold (4°C) trichloroacetic acid (TCA, 50%) was gently layered on the top of growth medium in each well to make a final TCA concentration of 10%. The mixtures were incubated at 4°C for 1 hour, and then washed 5 times with tap water to remove TCA, growth medium, low-molecular-weight metabolites, and serum proteins. The plates were air dried overnight. Next, fixed cells were stained with 50 μL of SRB solution (0.4%, wt/vol) for 10 minutes. After staining, SRB solution was decanted, and plates were quickly rinsed 5 times with 1% acetic acid to remove unbound dye and air dried overnight. The cellular protein-bound SRB was then dissolved with 200 μL unbuffered Tris base (10 mM, pH 10.5) for 30 minutes on a rocking platform shaker, and absorbance at 540 nm was measured by a plate reader.

[000179] Percentage of cell survival was calculated by absorbance at 540 nm in testing wells divided by absorbance in negative control wells (medium without the test compound). Percentages of cell survival versus drug concentrations were plotted and the concentration of drug that inhibited cell growth by 50% (IC50) was determined by nonlinear regression using WinNonlin (Pharsight Corporation, Mountain View, CA).

Assay for Androgen Receptor Binding Affinity

[000180] The AR binding affinity of test compounds was determined by a radioligand competitive binding assay with cytosolic AR prepared from rat ventral prostates. The AR preparation was incubated with 1 nM of 3H-mibolerone (MIB), 1 μM of triamicinolone acetonide at 4oC for 18 hour, in the presence of increasing concentrations of the test compound (with the concentrations ranging from 10-1 nM to 104 nM) or in the absence of the compound. After incubation, the protein-bound radioactivity was separated from free radioactivity by HAP precipitation. The bound radioactivity was then extracted from HAP by ethanol, and counted in a Beckman LS6800 liquid scintillation counter (Beckman Instruments Inc., Palo Alto, CA). Nonspecific binding was determined separately by including 1,000 nM of unlabeled MIB in the incubate. The binding data was fitted to the equation B = B0 * [1 - C/(IC50 + C)] using WinNonlin. The concentration of test compound that displaced the specific

binding of 3H-MIB by 50% (IC50) was obtained, and the equilibrium binding constant (Ki) was calculated from Ki = Kd * IC50/(Kd + L), where Kd was the equilibrium dissociation constant of 3H-MIB (0.19 ± 0.01 nM as determined in preliminary experiments) and L was the concentration of 3H-MIB used in the experiment (1 nM).

EXAMPLE 2

EFFECT OF HALOACETAMIDE SUBSTITUTED COMPOUNDS IN DIFFERENT CELL LINES

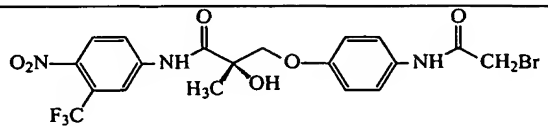
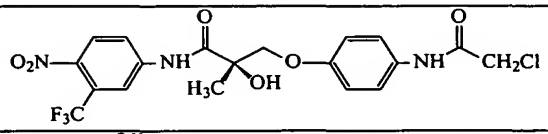
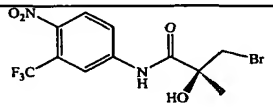
[000181] **METHODS:** LNCaP, DU145, PC-3, TSU, and PPC-1 cells were cultured in 96-well plates and treated with increasing concentrations of the compound of interest for 4 days. Cell survival was determined by the sulforhodamine B assay and was plotted as a percentage of control (drug-free wells) versus drug concentration. The concentration of drug that inhibited cell growth by 50% (IC50) was determined by non-linear regression. Known anticancer drugs were used as cytotoxic positive controls.

[000182] **RESULTS:** The IC_{50}s of Compounds 1 and 2, as well as S-NTBA, 5-FU and Melphalan in prostate cancer cell lines DU 145, PC-3, TSU, PPC-1 and LNCaP are shown in Table 1. The cytotoxicity of compounds 1, 2 and S-NTBA in different cell lines are shown in Figure 1 A-C, respectively. Compounds 1 and 2 demonstrated IC_{50} values in the low micro-molar range in inhibiting the growth of all of five prostate cancer cell lines.

[000183] LNCaP cells (the only androgen receptor expressing cell line tested) were not more sensitive to compounds 1 and 2 than other cell lines, suggesting that the growth inhibition effect was not related to the androgen receptor. The IC_{50}s from one-day treatment and 4 or 6 days treatment did not show significant difference, indicating that the growth inhibitory activity of these compounds was not likely a reversible process.

[000184] These studies indicated that compounds 1 and 2 may have potential as chemotherapeutic agents for the treatment of prostate cancer.

TABLE 1 – Prostate Cancer Cell Lines

Name	Structure	Prostate Cancer Cell Lines				
		DU145	PC-3	TSU	PPC-1	LNCaP
Compound 1 (μM)		1.3±0.3	2.41±0.6	0.4±0.3	1.1±0.1	1.1±0.2
Compound 2 (μM)		0.9±0.1	4.2±0.2	1.4±0.4	1.8±0.1	4.4±0.8
S-NTBA (μM)		4.7±0.3	3.1±0.5	3.5±0.2	2.2±0.2	1.3±0.2
5-FU (μM)		2.6±0.9	12.1±0.9	2.9±0.9	5.5±0.3	0.9±0.3
Melphalan (nM)		31.0±4.8	30.4±3.1	4.0±0.2	16.2±1.8	10.3±0.1

EXAMPLE 3

ANDROGEN RECEPTOR BINDING AFFINITIES

[000185] The Androgen Receptor binding affinities of compounds 1 and 2, as well as S-NTBAn are shown in Table 2.

TABLE 2:

Compound	Ki (nM)
1	13.9±1.4
2	1.9±0.3
S-NTBA	34.0±2.2

[000186] The results show that there is no relationship between the androgen receptor expression of the cell lines, androgen receptor binding affinity, and growth inhibitory activity of the compounds, indicating that the growth inhibitory properties of these compounds were likely not mediated by the androgen receptor.

EXAMPLE 4

EFFECT OF HALOACETAMIDE SUBSTITUTED COMPOUNDS ON CELL GROWTH

GROWTH CURVE:

[000187] **MATERIALS:** DMSO is the vehicle control and the solvent for Compound 1 and Compound 2.

[000188] **METHODS:** Cells were plated at 5-10 × 10^4 cells/well in five 6-well plates and incubated at 37°C, 5% CO_2 for 24 h to allow the cells sufficient time to attach and be in log phase growth at the start of the experiment. The media was aspirated from four of the plates and replaced with media containing vehicle control (DMSO) or drug dissolved in DMSO. The total volume of DMSO/drug added to each well was equal to 0.1% of the media volume in each well. LNCaP, PC-3, MCF-7, and CV-1 cells were treated with vehicle control, and increasing concentrations of Compound 1 and Compound 2 (0.01, 0.05, 0.1, 0.5, 1.0, 5.0, and 10.0 μM). Three wells were treated with the same concentration of the drugs or DMSO for each treatment condition listed above. The cells from the remaining 6-well plate were collected and counted to determine plating efficiency. The 6-well plates containing DMSO/drug were incubated for 120 h at 37°C, 5% CO_2. After 120 h, the media from each well was collected along with trypsinized cells and centrifuged at 150 × *g* for 4 min. The cells were resuspended in 1 mL of media, from which 90 μl was taken and combined with 10 μl trypan blue for counting on a hemacytometer.

[000189] **RESULTS:** The results are presented in Figure 2. Results indicate that the haloacetamides are potent cytotoxic agents. Compound 1 exhibits non-selective growth

inhibitory activity against various cancer cell lines in vitro where LNCaP (AR-dependent) cells are inhibited by approximately the same molar concentration of Compound 1 as the PC-3, MCF-7 and CV-1 cells (which are prostate, breast, and monkey kidney cell lines, respectively, none of which are dependent on the AR for growth) (Figure 2A). Compound 2 appears to exhibit some selectivity in that the AR-dependent LNCaP cells are approximately 10-fold more sensitive than the PC-3 or CV-1 cells (non AR-dependent). Only at very high concentrations (i.e. >5 micromolar) are the MCF-7 cells sensitive to Compound 2 (Figure 2B).

TUNNEL ASSAY:

[000190] **MATERIALS:** *In Situ* Cell Death Detection Kit, Fluorescein (Roche).

[000191] **METHODS:** DNA fragmentation of apoptotic cells was monitored by the TUNEL assay as described by the supplier. Briefly, LNCaP cells were plated at 2×10^5 cells/well in 2-well chamber slides and incubated at 37°C, 5% CO_2 for 24 h to allow the cells sufficient time to attach and be in log phase growth at the start of the experiment. The media was aspirated and replaced with media containing vehicle control (DMSO) or drug dissolved in DMSO. The total volume of DMSO/drug added to each well was equal to 0.1% of the media volume in each well. LNCaP cells were treated with vehicle control, and increasing concentrations of Compound 1 and Compound 2 (0.1, 1.0, and 10.0 μM) for 24-48 h. Two wells were treated with the same concentration of the drugs or DMSO for each treatment condition listed above. The media was collected along with the trypsinized cells and centrifuged at 150 × *g* for 4 min. The cells were resuspended in 50 μl PBS, pipetted onto poly-lysine coated slides, and then fixed in 4% methanol-free formaldehyde in PBS (pH 7.4) for 25 min at 4°C. Cells were permeabilized in 0.2% Triton X-100 in PBS for 5 min at room temperature. Terminal deoxynucleotidyl transferase labeling of 3'-ends of DNA strand breaks was performed using fluorescein-12-dUTP with an apoptosis detection system. Following end labeling, cells were then washed with PBS containing 0.1% Triton X-100 and 5 mg/ml albumin from bovine serum (BSA). All cells were stained with 1 μg/ml propidium iodide for 15

min. Green and red fluorescence emissions were observed microscopically using 520 nm and >620 nm filters, respectively.

[000192] **RESULTS:** The TUNEL assay is used to determine whether cells are undergoing apoptosis (cell death mechanism) as a result of drug treatment. During apoptosis the DNA of affected cells is fragmented, leaving 3' and 5' ends exposed. TUNEL assay incorporates a dye that labels the 3' ends of such DNA fragments which are then visualized by fluorescence. Results show that cells exposed to Compound 1 for 24 hours exhibit green fluorescence (relative to the 0.1% DMSO vehicle control cells) (Figures 3A and B). The green fluorescene demonstrates that the cells have fragmented DNA and are undergoing apoptosis. There are also fewer cells stained with propidium iodide (relative to vehicle control) which is a further indication that many of the cells have died and floated away. Results for Compound 2 were similar (data not shown).

[000193] Without wishing to be bound to any particular mechanism or theory, one possible mechanism of action for haloacetamide compounds such as compounds 1 and 2 is that they alkylate cellular nucleophiles, the brominated derivative (Compound 1) being more potent (more reactive) than the chlorinated derivative (Compound 2), thus requiring a higher concentration of Compound 2 before apoptosis is initiated. The cellular concentration may be increased if the compounds utilize the AR to penetrate the cell. LNCaP cells, bearing AR, would increase the intracellular concentration more rapidly than the non-AR bearing cells.

[000194] It will be appreciated by a person skilled in the art that the present invention is not limited by what has been particularly shown and described hereinabove. Rather, the scope of the invention is defined by the claims that follow: